Effect of Abuse-Deterrent Formulations and IR Opioids on Abuse, Overdose and Death from Rx Opioids

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Professor, University of Colorado
Competing Interest Statement

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

Conflict of Interest Statement
- Many manufacturers of prescription opioids or stimulants as well as federal agencies subscribe to RADARS System.
- RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado.
- 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 company.
What is the Problem We Need to Solve?

Filling the Balloon

Person in Pain

Susceptible Person

Recreational Abuser

Abuse of Other Drugs

Intact → Chewed → Crushed

Outcomes

Addiction
Overdose
Death
## Alternate Route = Higher Risk of Major Effect

<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>

Progression of Prescription Opioid Abuse

The Balloon

Intact ► Chewed ► Crushed

- A
- D
- F

Outcomes

- OUD
- OD
- Treat

Susceptible Person

Guidelines

Enforcement

Recreational Abuser

Abuse of Other Drugs

Person in Pain

Heroin

Treat

PDMP
Prescription Opioid Abuse is Declining in the US

Trends in Opioid Analgesic Abuse and Mortality in the United States.
Deaths in National Vital Statistics System Decreasing! (excl heroin & illicit fentanyl)
10 FDA-approved ADFs: All physical/chemical or agonist/antagonist

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug Substance</th>
<th>Sponsor</th>
<th>Approval</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycontin</td>
<td>oxycodone</td>
<td>Purdue</td>
<td>4/4/2010</td>
<td>YES</td>
</tr>
<tr>
<td>Targiniq ER</td>
<td>oxycodone + naloxone</td>
<td>Purdue</td>
<td>7/23/2014</td>
<td>NO</td>
</tr>
<tr>
<td>Embeda</td>
<td>morphine + naltrexone</td>
<td>Pfizer</td>
<td>10/17/2014</td>
<td>YES</td>
</tr>
<tr>
<td>Hysingla ER</td>
<td>hydrocodone</td>
<td>Purdue</td>
<td>11/20/2014</td>
<td>YES</td>
</tr>
<tr>
<td>Morphabond</td>
<td>morphine</td>
<td>Inspirion</td>
<td>10/2/2015</td>
<td>NO</td>
</tr>
<tr>
<td>Xtampza ER</td>
<td>oxycodone</td>
<td>Collegium</td>
<td>11/6/2015</td>
<td>YES</td>
</tr>
<tr>
<td>Troxyca ER</td>
<td>oxycodone + naltrexone</td>
<td>Pfizer</td>
<td>8/22/2016</td>
<td>NO</td>
</tr>
<tr>
<td>Arymo ER</td>
<td>morphine</td>
<td>Egalet</td>
<td>1/9/2017</td>
<td>Limited</td>
</tr>
<tr>
<td>Vantrela ER</td>
<td>hydrocodone</td>
<td>Teva</td>
<td>1/18/2017</td>
<td>NO</td>
</tr>
<tr>
<td>RoxyBond</td>
<td>oxycodone</td>
<td>Inspirion</td>
<td>4/26/2017</td>
<td>NO</td>
</tr>
</tbody>
</table>
Systematic Review of Abuse Deterrent (Tamper Resistant) Formulations

- Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?
- 45 reports on opioids with abuse deterrent labeling
  - Hydrocodone (n=7)
  - Morphine (n=5)
  - Oxycodone (n=32)*
- Hill Criteria
- Also assessed confounding factors and bias

Cases Involving Intentional Abuse, Poison Center Program

- Effect Size
- Temporality
- Specificity

Reformulation

Change from baseline average (%) vs. Year and Quarter (2010-2015)

- OxyContin®
- Hydrocodone
- Hydromorphone
- IR oxycodone
- Morphine
- Other opioids group
Investigations Opened, Drug Diversion Program

- Effect Size
- Temporality
- Specificity

![Graph showing changes in drug reformulation over years and quarters.](image)
Drugs Used in Past 30 Days, Opioid Treatment Program

- Effect Size
- Temporality
- Specificity
Drugs Used in Past 30 Days, Survey of Key Informant Patients

- Effect Size
- Temporality
- Specificity
- Consistency

Reformulation

Change from baseline average (%)

Year and Quarter

Pre ORF 2010 2011 2012 2013 2014 2015

OxyContin
Hydrocodone
Hydromorphone
IR oxycodeone
Morphine
Other opioids group
Reported Change in Treatment Measures of Abuse After Reformulation of Oxycodone ER

Sample Size

Severtson 2016  24,049
Cicero 2012    2,566
Severtson 2016  12,438
Sankey 2016    365
Cicero 2015    10,784
Butler 2012    140,496
Cassidy 2014   232,874

Rate Ratio, Change in Abuse after Reformulation

-100%  -80%  -60%  -40%  -20%   0%   20%  40%  60%  80%
Client visits per month, Sydney Medically Supervised Injecting Centre

Degenhardt et al., Drug Alc Dependence 2015; 151: 56-57.

Past year nonmedical use estimate
Numbers in thousands

Year

Reformulation
Institute for Clinical and Economic Review (ICER)
Overall Approach

• Compared a hypothetical cohort of 100,000 adult non-cancer chronic pain patients who were newly prescribed either:
  a) extended-release (ER) ADF opioids, or
  b) ER non-ADF opioids

• Time horizon: 5 years (with 1 year cycle length)

• Perspective: third-party payer covering commercially-insured population
2. For a patient being considered for a prescription of an extended release opioid, is the evidence adequate to demonstrate a reduced risk of abuse for patients using OxyContin versus non-ADF extended release opioids?

| Yes: 9 | No: 3 |
Summary

- Our results suggest ADF opioids substantially reduce incidence of opioid abuse relative to non-ADF formulations among patients initially prescribed these drugs for therapeutic purposes, but with increased costs to the health system.

- Further research is required to ascertain how the balance of reduced diversion of prescribed opioids versus increased use of other legal and illicit opioids affects clinical and economic outcomes in these populations.
Societal cost savings from abuse deterrent formulations for prescription opioids in Canada

Conclusion
The expected reduction in the NMU rate for RxO that would result from mandating adoption of ADF across all opioids, would very likely produce significant net societal cost savings.
Results Skinner, 2017

• Total Canadian societal economic costs from non-medical use of prescription opioids - $4.3 billion/year.

• The median ADF effectiveness reducing NMU rates by between 45.1% and 64%.

• 2012 to 2015 savings ranged from $560 million to $16.9 billion ($140 million to $4.2 billion per year).

• Median estimate about $9.3 billion for the entire period (averaging $2.3 billion per year).

Summary

• Reformulation of oxycodone ER was followed by improved outcomes specific to oxycodone ER
• The initial decrease contrasted with increases for most other opioids during the first 18 months, but was then followed by decreases for almost all opioids
• Similar results in 3 different countries with different baseline conditions, measurements and timeframes
• Multiple sources of bias and confounding are present, but are different among data sources
• We need wider application of abuse deterrent preparations, particularly for immediate release products.