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

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RADARS® System
Competing Interests

• RADARS System is owned by Denver Health and Hospital Authority, the public hospital for the City and County of Denver. The program is supported by subscriptions by pharmaceutical manufacturers of prescription opioid and stimulants.
Goals

• Describe types of abuse-deterrent formulations (ADFs)
• Trends in abuse and overdose rates of extended-release (ER) opioids as abuse-deterrent formulations (ADFs) were introduced into the group
• Role of immediate release (IR) and ER opioids in prescription opioid abuse and overdose
• Predict the public health implications of ADF opioid products
FIGURE 2. Drug overdose deaths* involving opioids,†,§ by type of opioid¶ — United States, 2000–2014

Drugs overdose deaths involving opioids'
- Natural and semisynthetic opioids
- Synthetic opioids excluding methadone
- Methadone
- Heroin

Most Opioids

Progression of Rx Drug Abuse

Filling the Balloon

1. Person in Pain
   - Susceptible Person
2. Recreational Abuser
   - Abuse of Other Drugs

Intact → Chewed → Crushed

Outcomes
- Addiction
- Overdose
- Death
Who Cares About Chewing?

RADARS SKIP - Adults meeting DSM-IV criteria for substance abuse with a primary drug that is an opioid


Route among past month abuse (%)
Progression of Rx Drug Abuse

Emptying the Balloon

Person in Pain
Guidelines
Susceptible Person
Recreational Abuser
Abuse of Other Drugs

Outcomes
Addiction
Overdose
Death

Treatment

Intact
Chewed
Crushed

ADF
ADF
ADF

N
### 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>Arimy 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>
Most Opioids Available in US are IR

IR and ER/LA Opioid

Nationally estimated number of prescriptions dispensed for selected IR and ER/LA opioid analgesics from U.S. outpatient retail pharmacies

Source: IMS Health, National Prescription Audit™ Extracted May and August 2015
IR Opioids Abused Preferentially
Preferences in abuse of IR vs ER opioids in treatment-seeking opioid abusers

Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?

44 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

Change from baseline average (%)

Year and Quarter

Reformulation
Investigations Opened, Drug Diversion Program

- Effect Size
- Temporality
- Specificity

Change from baseline average (%)

Year and Quarter

Reformulation
Drugs Used in Past 30 Days, Opioid Treatment Program

![Graph showing changes in drug use over time.](chart)

- **Effect Size**
- **Temporality**
- **Specificity**

The graph illustrates the percentage change from baseline for various opioids over the years, highlighting the impact of reformulation on drug usage.
Drugs Used in Past 30 Days, Survey of Key Informant Patients

- Effect Size
- Temporality
- Specificity
- Consistency

Change from baseline average (%)

Year and Quarter

Reformulation

Pre ORF  2010  2011  2012  2013  2014  2015

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Rate Ratio, Change in Abuse after Reformulation</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severtson 2016</td>
<td>24,049</td>
<td>-60%</td>
<td>3</td>
</tr>
<tr>
<td>Cicero 2012</td>
<td>2,566</td>
<td>-80%</td>
<td>14</td>
</tr>
<tr>
<td>Severtson 2016</td>
<td>12,438</td>
<td>-80%</td>
<td>12</td>
</tr>
<tr>
<td>Sankey 2016</td>
<td>365</td>
<td>-60%</td>
<td>12</td>
</tr>
<tr>
<td>Cicero 2015</td>
<td>10,784</td>
<td>-60%</td>
<td>12</td>
</tr>
<tr>
<td>Butler 2012</td>
<td>140,496</td>
<td>-40%</td>
<td>14</td>
</tr>
<tr>
<td>Cassidy 2014</td>
<td>232,874</td>
<td>-80%</td>
<td>31</td>
</tr>
</tbody>
</table>

Legend:
- oxycodone ER
- other opioids
- fentanyl & hydromorphone
- morphine
- heroin
- ER morphine
- ER oxymorphone +246%
Client visits per month, Sydney Medically Supervised Injecting Centre


Past year nonmedical use estimate
Numbers in thousands

Year

Reformulation
Timeline of Interventions vs. Oxycodone ER

Rate adjusted for population

Percent of Population Covered by PDMP

Timeline of Interventions vs. Oxycodone ER

WA Rx Guidelines
National Drug Take Back
Oxycodone ER Reformulation
FL
TIRF REMS
ER/LA REMS
HC-APAP Tramadol
CDC Pain Guideline

Oxycodone ER

PDMP

Other Opioids

All Other Opioids (per 100,000 population)  Oxycodone ER (per 10,000 population)  PDMP Coverage
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
Results: Cost Neutrality Threshold Analysis

• In 2\textsuperscript{nd} threshold analysis, varied ADF opioid drug cost to achieve cost-neutrality
  • Kept base case incidence of abuse in each opioid cohort constant
• Average daily ADF opioid costs would need to be reduced from $11.60 to $7.04 at 90mg MED per day to achieve cost neutrality
  • 39% discount from current pricing

<table>
<thead>
<tr>
<th>Drug Cost Category</th>
<th>Base-case cost</th>
<th>Cost to attain cost-neutrality</th>
<th>Percentage difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADF opioid average daily drug cost*</td>
<td>$11.60</td>
<td>$7.04</td>
<td>-39.3%</td>
</tr>
</tbody>
</table>

\*Indicates drug cost per day at 90mg MED daily dose

NOTE: Based on initial draft report, subject to change
Scenario Analysis: Diversion

- Using estimate of 1.25 cases of diverted abuse for every case of prescription opioid abuse, ADF cohort has additional spending of ~$521 million over 5 years.

- To achieve cost-neutrality, diversion in the ADF cohort would need to decrease by approximately 57% relative to the non-ADF cohort.

- Reducing the rate of diversion to 1:1 and 0.75:1 ratios required greater reductions in diversion risk to achieve cost neutrality.
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.
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
• We conclude that the evidence available doesn’t indicate this affected the results.
• We need wider application of abuse deterrent preparations, particularly for immediate release products.
Questions?