Real World Data: Do ADFs Change Behavior?

What Current Opioid Data Imply for Stimulants in the Future

Janetta L. Iwanicki, MD
Scientific Director of Research and Surveillance
RADARS, Rocky Mountain Poison & Drug Center
Roadmap

• Real-world data on ADF effectiveness

• Opana ER and its complicated history

• Effects of policy on behavior and trends

• Current prescription stimulant real-world data

• Lessons learned
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

PDMP

Intact
Chewed
 Crushed

Outcomes
Addiction
Overdose
Death

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
Temporality: 3 Phases of Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010 – 2016Q2
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
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>
</tr>
<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

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

![Graphs showing the rate per 100,000 population over time for different formulations and opioid types.](image)
Alternate Explanations Fail the Temporality and Specificity Criteria

Oxycodone ER
All Other Opioids

↑ PDMP Initiation
Opana ER

- Extended-release oxymorphone

- Oxymorphone developed in Germany 1914

- Patented 1955

- Opana ER formulation Initially approved in 2006

- Indications: moderate to severe pain requiring around-the-clock treatment

- Geographic distribution
Opana ER: Geographic distribution and heterogeneity

**Time:** 2009q3 – 2016q4  
**Source:** IQVIA  
**N:** 360,432,541 units dispensed  
**Analysis unit:** 3-digit ZIP  
**Metric:** cumulative population-adjusted rate
Oxymorphone

• Poor oral bioavailability
  – 10x more potent intravenously than orally

• Leads to unusual behaviors
  • Single 40mg pill = split into quarters
  • Each quarter = 2-4 users
  • Single pill leads to 8-16 doses intravenously
  • Each dose 50-75 MME
Oxymorphone

• Poor oral bioavailability
  – 10x more potent intravenously than orally

• Leads to unusual behaviors
  – Drug sharing
  – Unsafe injection practices

• Complications
  – HIV
  – Hepatitis C
  – TTP
Opana ER: Interventions and Policy Changes

• 2011: Reformulation approved
  – Released in 2012
  – Tamper resistant, but did not achieve ADF labeling

• Concern for transition from intranasal to intravenous abuse

• Outbreaks associated with oxymorphone
Opana ER: Interventions and Policy Changes

- March 2017:
  - FDA meeting
  - 18-8 vote, benefits no longer outweigh risks
- June 2017:
  - Recommended to be removed from market
- July 2017:
  - Opana ER removed
  - No change to generic forms or IR
Oxymorphone: Big picture
Poison Center Program

Per 100,000 population

- Oxycodone
- Fentanyl
- Hydrocodone
- Hydromorphone
- Morphine
- Oxymorphone
- Methadone
- Buprenorphine
- Tramadol
- Tapentadol
Opana ER: Effects of Policy on Behavior and Trends
Poison Center Program, rate per population

All Oxymorphone

2012

2017
Opana ER: Effects of Policy on Behavior and Trends
Poison Center Program, rate per prescriptions

2012

2017

Oxymorphone IR

Opana ER

References: 10 pt.
Opana ER: Effects of Policy on Behavior and Trends
Treatment Center Programs, rate per population

All Oxymorphone

Oxymorphone IR

Opana ER

References: 10 pt.
Opana ER: Effects of Policy on Behavior and Trends Treatment Center Programs, rate per prescriptions
Opana ER: Effects of Policy on Behavior and Trends
Drug Diversion Program, rate per population
Opana ER: Effects of Policy on Behavior and Trends
Drug Diversion Program, rate per prescriptions

References: 10 pt.
Opana ER: Effects of Policy on Behavior and Trends
Did injection behavior change?
Opana ER: Effects of Policy on Behavior and Trends
Did injection behavior change?
Opana ER: Effects of Policy on Behavior and Trends

Did injection behavior change? NMURx data

<table>
<thead>
<tr>
<th>Route of Nonmedical Use</th>
<th>Number of Adults in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>573092</td>
</tr>
<tr>
<td>Oral</td>
<td>497964</td>
</tr>
<tr>
<td>Inhalation</td>
<td>185358</td>
</tr>
<tr>
<td>Injection</td>
<td>106705</td>
</tr>
</tbody>
</table>

References: 10 pt.
Stimulants

• Used as single substance or polysubstance
  • Pharmaceutical "speedball" effect
• Highest rates in teenage and young adult population
• Rates of intentional abuse stable, but diversion increasing
Stimulants, RADARS Poison Centers

References: RADARS PC 3Q2017, intentional abuse cases
Stimulants, RADARS Drug Diversion

- Methylphenidate
- Amphetamine

Graph showing the concentration per 100,000 population from 2007 to 2017.
Prescription Stimulants: Prevalence of Nonmedical Use

NMURx data

<table>
<thead>
<tr>
<th>Route of Nonmedical Use</th>
<th>Prevalence of Nonmedical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2.08</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>1.57</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>0.17</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0.32</td>
</tr>
<tr>
<td>Modafinil</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Prescription Stimulants: Routes of Nonmedical Use NMURx data

![Bar chart showing the proportion of past year nonmedical users for different routes of nonmedical use. The highest proportion is for swallowed, at 85.1%, followed by crushed (24.5%), dissolve (20.3%), inhaled (21.6%), and injection (12.1%).]
Prescription Stimulants: Routes of Nonmedical Use
NMURx data

<table>
<thead>
<tr>
<th>Route of Nonmedical Use</th>
<th>Swallowed</th>
<th>Crushed/Chewed</th>
<th>Dissolved in Mouth</th>
<th>Inhaled</th>
<th>Injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>87.8</td>
<td>18.6</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>50.2</td>
<td>31.1</td>
<td>32.9</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>83.3</td>
<td>37.9</td>
<td>23.5</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Modafinil</td>
<td>63.1</td>
<td>22.9</td>
<td>28.5</td>
<td>6.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Proportion of Past Year Nonmedical Users

References: 10 pt.
Conclusions

• ADF preparations do appear to decrease overall abuse
  – Biggest impact likely in those who do not yet have severe opioid use disorder

• ADF preparations may impact route of abuse
  – Transition from IN to IV seen with oxymorphone

• Oxymorphone as a molecule lends itself to dangerous behaviors
  – Low oral bioavailability, high intravenous potency
  – Sharing behaviors are common
Conclusions and Discussion

• Rising prescription stimulant nonmedical use, abuse, diversion
  – Approx 5 million adults in US currently nonmedically use
  – Potential for early warning of issues to come

• Trajectories of stimulant use poorly understood
  – Will the balloon apply?

• Non-oral routes of stimulant abuse suggest potential for ADF utility
  – Will need to address both inhalation and injection
  – Beware unintended consequences
Questions?

Janetta.Iwanicki@RMPDC.org