Unintentional Drug Death

Unintentional Drug Overdose Deaths by Major Type of Drug, United States, 1999-2008

Number of Deaths

15,000
11,000
7,000
3,000


Opioid Analgesic  Cocaine  Heroin
The Prescription Drug Abuse Epidemic

40% of Opioid Analgesic Deaths

- Methadone, 16.2%
- Other opioid painkillers, 22.0%
- Benzo./antidepress, 6.5%
- Cocaine, 25.1%
- Heroin, 7.7%
- Meth / amphet., 6.4%
- Other specified drugs, 16.1%

Paulozzi, CDC www.deadiversion.usdoj.gov/arco/retail_drug_summary/index.html
Moving Forward: USA

• Pharmaceutical strategies
  – Improve physical tamper resistance (i.e. OxyContin®, Exalgo®)
  – Incorporate deterrent (i.e. Suboxone®, Embeda®)

• Regulatory strategies
  – REMS: FDA Approval of Extended Release (ER) & Long Acting (LA) opioid Risk Evaluation Mitigation Strategy (REMS) in July 2012; other class-wide REMS in draft
  – Prescription Monitoring Programs (PMP) across US

• Measuring impact of these strategies
  – RADARS® System Data Trending
  – Mosaic approach
Prescription Opioid Misuse & Diversion

• United States Experience
  – Deaths from opioid abuse have surpassed deaths caused by motor vehicle accidents
  – Abuse deterrent formulations
  – Increasing availability of generic products
  – Toll of accidental pediatric exposures

• Outline of Presentation
  – RADARS® System Methodology & General Results
  – Trends with abuse deterrent formulations & market changes
  – Medical outcomes following pediatric exposures
  – Lessons learned
What is the RADARS® System?

• History
  – 2001, created by Purdue Pharma
  – 2006, Denver Health and Hospital Authority
    • Multiple pharmaceutical subscribers
    • Independent program
    • Denver Public Safety Net Hospital for 150 years
    • State sanctioned independent authority

• Purpose
  – Measure rates of misuse, abuse and diversion of prescription drugs
Mosaic Approach to Surveillance

- **Poison Center**: Acute Events 51 Centers 47 States
- **Drug Diversion**: Criminal Justice 280 investigator 50 states
- **Opioid Tx Program (OTP)**: Patients in Tx 73 programs 33 states
- **Survey of Key Informants’ Patients (SKIP)**: Patients in Tx 125 practices 50 states
- **College Survey**: 2000 students 50 States 3x each year
- **StreetRx**
  - www.streetrx.com
  - Users/Buyers Crowdsourcing 50 states

**Patients in Tx**
- Opioid Tx Program (OTP): 73 programs 33 states
- Survey of Key Informants’ Patients (SKIP): 125 practices 50 states

**States**
- Poisen Center: 47 states
- Drug Diversion: 50 states
- Opioid Tx Program (OTP): 33 states
- Survey of Key Informants’ Patients (SKIP): 50 states
- College Survey: 50 states

**Users/Buyers Crowdsourcing**
- StreetRx: 50 states
RADARS® System Process
A Tale of Two Denominators

POPULATION RATE = \frac{Counts \ by \ System}{US \ Population}
  
  • Disease burden on whole population
  • Does not account for drug availability

UNIQUE RECIPIENTS OF DISPENSED DRUG (URDD) RATE = \frac{Counts \ by \ System}{URDD}

  • Number of unique people filling prescription for drug (refills excluded)
## RADARS System Opioid Abuse Population Rate (Ranked Highest-Lowest) 2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>Poison Center</th>
<th>Opioid Treatment</th>
<th>Survey of Key Informant Pts</th>
<th>Drug Diversion</th>
<th>College Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrocodone</td>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>Oxycodone</td>
<td>Hydrocodone</td>
</tr>
<tr>
<td>2</td>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>3</td>
<td>Tramadol</td>
<td>Methadone</td>
<td>Morphine</td>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>4</td>
<td>Methadone</td>
<td>Morphine</td>
<td>Hydromorphone</td>
<td>Buprenorphine</td>
<td>Tramadol</td>
</tr>
<tr>
<td>5</td>
<td>Morphine</td>
<td>Hydromorphone</td>
<td>Methadone</td>
<td>Methadone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>6</td>
<td>Buprenorphine</td>
<td>Buprenorphine</td>
<td>Buprenorphine</td>
<td>Hydromorphone</td>
<td>Methadone</td>
</tr>
<tr>
<td>7</td>
<td>Fentanyl</td>
<td>Fentanyl</td>
<td>Fentanyl</td>
<td>Tramadol</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>8</td>
<td>Hydromorphone</td>
<td>Tramadol</td>
<td>Tramadol</td>
<td>Fentanyl</td>
<td>Hydromorphone</td>
</tr>
</tbody>
</table>
# RADARS System Opioid Abuse
## URDD Rates (Ranked Highest-Lowest) 2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>Poison Center</th>
<th>Opioid Treatment</th>
<th>Survey of Key Informant Pts</th>
<th>Drug Diversion</th>
<th>College Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methadone</td>
<td>Methadone</td>
<td>Hydromorphone</td>
<td>Methadone</td>
<td>Methadone</td>
</tr>
<tr>
<td>2</td>
<td>Buprenorphine</td>
<td>Hydromorphone</td>
<td>Methadone</td>
<td>Hydromorphone</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>3</td>
<td>Morphine</td>
<td>Morphine</td>
<td>Morphine</td>
<td>Buprenorphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>4</td>
<td>Hydromorphone</td>
<td>Buprenorphine</td>
<td>Buprenorphine</td>
<td>Morphine</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>5</td>
<td>Fentanyl</td>
<td>Fentanyl</td>
<td>Fentanyl</td>
<td>Oxycodone</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>6</td>
<td>Tramadol</td>
<td>Oxycodone</td>
<td>Oxycodone</td>
<td>Fentanyl</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>7</td>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>Hydrocodone</td>
<td>Hydrocodone</td>
<td>Hydrocodone</td>
</tr>
<tr>
<td>8</td>
<td>Hydrocodone</td>
<td>Tramadol</td>
<td>Tramadol</td>
<td>Tramadol</td>
<td>Tramadol</td>
</tr>
</tbody>
</table>
RADARS System Opioid Abuse Trends
Rates by Program, 2002-2012

Population

URDD
RADARS System Opioid Abuse Trends
Poison Center Program Intentional Exposures
2003 - 2011

Rate per 1,000 URDD

Quarter/Year

Buprenorphine
Fentanyl
Hydrocodone
Hydromorphone
Methadone
Morphine
Oxycodone
Oxymorphone

2002 2011
US CDC* Mortality Data

Drug-related deaths involving opioids, by type of opioid — Drug Abuse Warning Network Medical Examiner System, 13 states, 2009

<table>
<thead>
<tr>
<th>Opioid</th>
<th>No.</th>
<th>Death rate/100kg MME</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All deaths</td>
<td>Single drug deaths</td>
<td>All deaths</td>
<td>Single drug deaths</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>20</td>
<td>2</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>364</td>
<td>99</td>
<td>7.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>550</td>
<td>42</td>
<td>14.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>74</td>
<td>4</td>
<td>9.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Morphine</td>
<td>824</td>
<td>153</td>
<td>20.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1,097</td>
<td>150</td>
<td>8.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Methadone</td>
<td>1,034</td>
<td>298</td>
<td>33.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Total†</td>
<td>3,294</td>
<td>748</td>
<td>10.4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

MME = morphine milligram equivalent; RR = rate ratio; CI = confidence interval.
*Centers for Disease Control and Prevention
† Counts for each opioid might not sum to the total shown for all deaths because some deaths involved more than one opioid.

### CDC: 2009 Mortality Data Rank

<table>
<thead>
<tr>
<th>Rank</th>
<th>CDC Death rate/100kg MME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methadone</td>
</tr>
<tr>
<td>2</td>
<td>morphine</td>
</tr>
<tr>
<td>3</td>
<td>hydrocodone</td>
</tr>
<tr>
<td>4</td>
<td>hydromorphone</td>
</tr>
<tr>
<td>5</td>
<td>oxycodone</td>
</tr>
<tr>
<td>6</td>
<td>fentanyl</td>
</tr>
<tr>
<td>7</td>
<td>buprenorphine</td>
</tr>
</tbody>
</table>

MME = morphine milligram equivalent  
URDD = unique recipient of dispensed drug
RADARS System vs CDC
2009 Mortality Data Rank

<table>
<thead>
<tr>
<th>Rank</th>
<th>PC Program Rate/1,000 URDD</th>
<th>CDC Death rate/100kg MME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methadone</td>
<td>methadone</td>
</tr>
<tr>
<td>2</td>
<td>morphine</td>
<td>morphine</td>
</tr>
<tr>
<td>3</td>
<td>fentanyl</td>
<td>hydrocodone</td>
</tr>
<tr>
<td>4</td>
<td>buprenorphine</td>
<td>hydromorphone</td>
</tr>
<tr>
<td>5</td>
<td>hydromorphone</td>
<td>oxycodone</td>
</tr>
<tr>
<td>6</td>
<td>oxycodone</td>
<td>fentanyl</td>
</tr>
<tr>
<td>7</td>
<td>hydrocodone</td>
<td>buprenorphine</td>
</tr>
</tbody>
</table>

MME = morphine milligram equivalent
URDD = unique recipient of dispensed drug

*Spearman rank correlation is fairly strong (p=0.052) in the ranks of the two estimates.*
Abuse Deterrent Formulations
Effective Innovation or Marketing Gambit?

OxyContin  Suboxone
OxyContin® URDD Rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Δ(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>-52.9%</td>
</tr>
<tr>
<td>Other Opioids</td>
<td>-16.8%</td>
</tr>
</tbody>
</table>

URDD: Unique recipients of dispensed drug
OxyContin® URDD Rate

**Opioid Treatment Program**

<table>
<thead>
<tr>
<th>Year</th>
<th>Before Reformulation</th>
<th>After Reformulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008Q3</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>2009Q1</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>2009Q3</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>2010Q1</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>2010Q3</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>2011Q1</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>2011Q3</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>2012Q1</td>
<td>1.0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Survey of Key Informant Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Δ(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>-9.4%</td>
</tr>
<tr>
<td>Other Opioids</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

URDD: Unique recipients of dispensed drug
Route of OxyContin Abuse
Survey Key Informant Pts, 2008 - 2011

- Swallowed
- Other Routes

OxyContin OP Formulation Released
Increase in Oxycodone Population Rate is Driven by IR Formulation

Drug Diversion

Poison Centers
Reformulated OxyContin

Conclusions

• Data support that reformulated OxyContin is tamper and abuse deterrent
  – Poison Center abuse, Drug Diversion and Opioid Treatment Program cases have decreased
  – OxyContin rates decreased at a much higher percentage than other opioids over the same time period
  – Decrease in both Population and URDD rates suggests reduction in both availability and desirability

• New formulation still is abused
  – SKIP data show minimal effect

• Abuse of other drugs increasing
  – Net effect?

URDD: Unique recipients of dispensed drug; SKIP: Survey of key informants' patients
Availability of Buprenorphine has Expanded Unique Recipient of Dispensed Drug (URDD)

- Suboxone Tablets
- Suboxone Oral Film
- Total SI Buprenorphine
- Total Buprenorphine

URDD

2006 2012
Buprenorphine Rates
Poison Center, Drug Diversion Programs
Population Rate (2006 – 2012)

![Graph showing Buprenorphine Rates](image-url)
Survey Key Informants’ Patients
Population v. URDD Rate, 2010 Q1 - 2012 Q1

Population rate per 100,000

2010 2012

Total buprenorphine
SI buprenorphine tablets
Not otherwise specified buprenorphine
Suboxone® tablets
Suboxone® oral film

URDD rate per 1,000

2010 2012

Total buprenorphine
SI buprenorphine tablets
Suboxone® tablets
Suboxone® oral film
RADARS® System
Poison Center Program – Exposure Rates and Medical Outcomes in Children
Poison Center Program
Unintentional General, Population and URDD Rates
Children 0-12 Years (2009 Q4 – 2012Q1)

Rate per 100,000 Population

Rate per 1,000 URDD

- Single ingredient buprenorphine
- Suboxone
- Suboxone Oral Film

Removed
The Underrecognized Toll of Prescription Opioid Abuse on Young Children

J. Elise Bailey, MSPH
Elizabeth Campagna, MS
Richard C. Dart, MD, PhD
The RADARS System Poison Center Investigators*

From the Rocky Mountain Poison and Drug Center–Denver Health, Denver, CO (Bailey, Campagna, Dart); and the University of Colorado School of Medicine, Denver, CO (Dart).

Bailey et al

Table 1. Characteristics and outcomes of childhood (<6 years of age) exposures by opioid analgesic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buprenorphine (n=176)</th>
<th>Fentanyl (n=123)</th>
<th>Hydrocodone (n=6,003)</th>
<th>Hydromorphone (n=68)</th>
<th>Methadone (n=415)</th>
<th>Morphine (n=419)</th>
<th>Oxycodone (n=2,036)</th>
<th>Total (n=9,240)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (0.8-5.0)</td>
<td>1.9 (0.2-5.0)</td>
<td>2.0 (0.0-5.5)</td>
<td>2.0 (0.8-5.0)</td>
<td>2.0 (0.1-5.0)</td>
<td>2.0 (0.1-5.0)</td>
<td>2.0 (0.1-5.5)</td>
<td>2.0 (0.0-5.5)</td>
</tr>
<tr>
<td>Male, No. (%)*</td>
<td>99 (56.3)</td>
<td>64 (52.5)</td>
<td>3,232 (53.9)</td>
<td>33 (48.5)</td>
<td>232 (56.7)</td>
<td>224 (53.5)</td>
<td>1,081 (53.5)</td>
<td>4,965 (53.9)</td>
</tr>
<tr>
<td><strong>Outcome, No. (%)†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No effect</td>
<td>40 (32.0)</td>
<td>51 (64.6)</td>
<td>2,673 (77.3)</td>
<td>32 (74.4)</td>
<td>173 (62.2)</td>
<td>171 (64.8)</td>
<td>916 (78.4)</td>
<td>4,056 (74.9)</td>
</tr>
<tr>
<td>Minor effect</td>
<td>55 (44.0)</td>
<td>17 (21.5)</td>
<td>708 (20.5)</td>
<td>11 (25.6)</td>
<td>55 (19.8)</td>
<td>64 (24.2)</td>
<td>186 (15.8)</td>
<td>1,096 (20.2)</td>
</tr>
<tr>
<td>Moderate effect</td>
<td>25 (20.0)</td>
<td>8 (10.1)</td>
<td>71 (2.1)</td>
<td>0</td>
<td>34 (12.2)</td>
<td>24 (9.1)</td>
<td>52 (4.4)</td>
<td>214 (4.0)</td>
</tr>
<tr>
<td>Major effect</td>
<td>5 (4.0)</td>
<td>3 (3.8)</td>
<td>6 (0.2)</td>
<td>0</td>
<td>14 (5.0)</td>
<td>5 (1.9)</td>
<td>10 (0.8)</td>
<td>43 (0.8)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0</td>
<td>0</td>
<td>2 (0.1)</td>
<td>0</td>
<td>2 (0.7)</td>
<td>0</td>
<td>4 (0.3)</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>Unknown§</td>
<td>47</td>
<td>44</td>
<td>2,385</td>
<td>22</td>
<td>127</td>
<td>136</td>
<td>779</td>
<td>3,540</td>
</tr>
<tr>
<td>Confirmed nonexposure</td>
<td>4</td>
<td>0</td>
<td>158</td>
<td>3</td>
<td>10</td>
<td>19</td>
<td>89</td>
<td>283</td>
</tr>
</tbody>
</table>
Buprenorphine Conclusions

- Has availability of buprenorphine expanded?
  - Dramatic increase in people filling a prescription (URDD)
  - Marked increase of misuse and abuse in all systems

- Is Suboxone an abuse deterrent formulation?
  - Yes, endorsements are falling and lower than single ingredient in most programs

- Misuse and abuse of buprenorphine in high risk populations (OTP and SKIP)
  - Total endorsements rising quickly
  - Single ingredient is generally preferred

URDD: Unique recipients of dispensed drug; OTP: Opioid treatment program; SKIP: Survey of key informants’ patients
StreetRx.com
## Prices for Any — Ontario

<table>
<thead>
<tr>
<th>Drug</th>
<th>Location</th>
<th>Price</th>
<th>Date</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyNEO, 10mg pill</td>
<td>Windsor, Ontario</td>
<td>$14</td>
<td>Oct 26</td>
<td></td>
</tr>
<tr>
<td>Percocet, 5mg pill</td>
<td>Ontario</td>
<td>$6</td>
<td>Oct 18</td>
<td></td>
</tr>
<tr>
<td>OxyNEO, 10mg pill</td>
<td>Belleville, Ontario</td>
<td>$10</td>
<td>Sep 24</td>
<td>Not Bad</td>
</tr>
<tr>
<td>Adderall XR, 5mg pill</td>
<td>Toronto, Ontario</td>
<td>$2</td>
<td>Sep 21</td>
<td></td>
</tr>
<tr>
<td>Hydromorph Contin, 6mg pill</td>
<td>Toronto, Ontario</td>
<td>$5</td>
<td>Jul 1</td>
<td></td>
</tr>
<tr>
<td>Hydromorph Contin, 18mg pill</td>
<td>Toronto, Ontario</td>
<td>$15</td>
<td>Jul 1</td>
<td></td>
</tr>
</tbody>
</table>
Street Price Quotient
OxyContin® Reformulation Analysis

The diagram shows a boxplot comparing the street price per milligram of IR Oxydalone, ER Oxydalone-original formulation, and Reformulated ER Oxydalone. The prices are indicated by the median and interquartile range. The red box represents the period before the introduction of reformulated ER oxycodone, the blue box during the transition to reformulated ER oxycodone, and the green box after the reformulated ER oxycodone transition. The prices are as follows:

- IR Oxydalone: $0.85 per milligram
- ER Oxydalone-original formulation: $0.97 per milligram
- Reformulated ER Oxydalone: $0.70 per milligram
RADARS® System
Intervention
Assessments
Operation UNITE

- Launched in 2003 to address prescription opioid abuse in Kentucky
- Three-pronged intervention
  - Education
  - Enforcement
  - Treatment
Rise in Abuse Less in Operation UNITE Region

The RADARS® System Poison Center Program
Intentional Abuse Population Rates – All Opioids
2nd Quarter 2006 to 4th Quarter 2011
Percent Change from Baseline
Rise in Abuse is Attenuated in States with PDMPs

• States **without** a PDMP
  – Poison Center cases: Increase 1.9% per quarter*
  – Opioid Treatment Program: Increase 4.9% per quarter

• States **with** a PDMP
  – Poison center cases increase at 0.2% per quarter
  – Opioid Treatment Program: Increase 2.6% per quarter

* All increases are percent increases per quarter, exponential, adjusted for population and unique recipients of a dispensed drug (URDD)

Summary

• Important to employ mosaic approach
  – No one data source is perfect
  – Different sources answer different questions
  – Triangulation and validation of external data sources

• Initial evidence supports that abuse deterrent formulations reduce abuse of those products
  – Dependent upon how drug is misused
  – Important to monitor consequence of “squeezing the balloon”

• Policy implications
  – Should formulations with higher abuse remain on market?
Thank You!

For further information or questions:

richard.dart@rmpdc.org

www.radars.org