TRENDS OF OPIOID MISUSE AND DIVERSION: LESSONS FOR EUROPE FROM THE USA

PROFESSOR ICRO MAREMMANI
University of Pisa, Italy

DR JODY GREEN
Rocky Mountain Poison and Drug Center, USA
WELCOME AND INTRODUCTIONS

PROFESSOR ICRO MAREMMA
University of Pisa, Italy
AGENDA

11:45–11:50 Welcome and Introductions
   Professor Icro Maremmani

11:50 –12:30 Trends of Opioid Misuse and Diversion: Lessons for Europe from the USA
   Dr Jody Green

12:30–12:45 Question and Answer Session
   Dr Jody Green
   Professor Icro Maremmani
• This symposium is sponsored by Reckitt Benckiser Pharmaceuticals (RBP)
• RBP had no influence on the scientific content of this presentation

• This presentation refers to medications that may not have been approved in all countries
• Please refer to your local prescribing information
TRENDS OF OPIOID MISUSE AND DIVERSION: LESSONS FOR EUROPE FROM THE USA

DR JODY GREEN
Rocky Mountain Poison and Drug Center, USA
Trends of Opioid Misuse and Diversion: Lessons for Europe from the United States

16 October 2012

Jody L. Green, PhD

Research Director – Rocky Mountain Poison and Drug Center
Assistant Professor – Vanderbilt University Medical Center
Disclosure for Dr Jody Green

In compliance with COI policy, ISAM requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Shareholder</th>
<th>No relevant conflicts of interest to declare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant / Research Support</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Consultant</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Paid Instructor</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Speaker bureau</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Other</td>
<td>Reckitt Benckiser Pharmaceuticals and other opioid manufacturers subscribe to the RADARS System</td>
</tr>
</tbody>
</table>
Opioids and the Stars
Some celebrities have been publicly linked with use of these powerful painkillers (in several cases, with more than one such medication).

Reported past users of OxyContin, generic oxycodone, or Percocet (which consists of oxycodone and acetaminophen):

Heath Ledger (actor; oxycodone was in his blood when he died)
Rush Limbaugh (radio talk show host)
Courtney Love (singer)

Reported past users of hydrocodone, which is chemically similar to oxycodone, including Vicodin (which consists of hydrocodone and acetaminophen):

Jamie Lee Curtis (actress)
Eminem (singer)
Brett Favre (retired football star)

Cindy McCain (businesswoman, wife of Sen. John McCain)
Winona Ryder (actress)
Steven Tyler (singer, American Idol judge)
Walter Payton (late football legend)
Matthew Perry (actor)
Nicole Richie (reality TV personality)
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/RMPDC
    • State sanctioned independent authority
    • Independently owned and operated program
    • Multiple pharmaceutical subscribers (cost-share model)
    • Scientific advisory board
    • Catalyst for bringing together industry, regulatory, academics

• 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: Users/Buyers Crowdsourcing
- www.streetrx.com
- 50 states
RADARS® System Process
A Tale of Two Denominators

**Drug Diversion**  **Poison Center**  **OTP**  **SKIP**  **College Survey**

**Numerators compiled by each program**

**POPULATION RATE** = \( \frac{\text{Counts by System}}{\text{US Population}} \)
- Disease burden on whole population
- Does not account for drug availability

**UNIQUE RECIPIENTS OF DISPENSED DRUG (URDD) RATE** = \( \frac{\text{Counts by System}}{\text{URDD}} \)
- Number of unique people filling prescription for drug (refills excluded)
### RADARS System Opioid Abuse Trends 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 Trends
## URDD Rates (Ranked Highest-Lowest)
### 2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>Poison Center</th>
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<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><strong>oxycodone</strong></td>
<td>buprenorphine</td>
</tr>
<tr>
<td>6</td>
<td>tramadol</td>
<td><strong>oxycodone</strong></td>
<td><strong>oxycodone</strong></td>
<td>fentanyl</td>
<td><strong>oxycodone</strong></td>
</tr>
<tr>
<td>7</td>
<td><strong>oxycodone</strong></td>
<td>hydrocodone</td>
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<td>hydrocodone</td>
<td>hydrocodone</td>
</tr>
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<td>tramadol</td>
<td>tramadol</td>
<td>tramadol</td>
<td>tramadol</td>
</tr>
</tbody>
</table>

*Note: The highlighted rows represent the most commonly reported opioids in each category.*
URDD: Unique recipients of dispensed drug
## RADARS System
### 2009 URDD Mortality Ranking

<table>
<thead>
<tr>
<th>Rank</th>
<th>RADARS System Rate/100,000 URDD</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>fentanyl</td>
</tr>
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<td>6</td>
<td>oxycodone</td>
</tr>
<tr>
<td>7</td>
<td>hydrocodone</td>
</tr>
</tbody>
</table>
## 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</td>
<td>Single drug deaths</td>
<td>All</td>
<td>Single drug deaths</td>
</tr>
<tr>
<td></td>
<td>deaths</td>
<td></td>
<td>deaths</td>
<td></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.

### RADARS System vs CDC 2009 Mortality Data

<table>
<thead>
<tr>
<th>Rank</th>
<th>RADARS System Rate/100,000 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>
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<td>fentanyl</td>
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<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”

- OxyContin
- Exalgo
- Suboxone
OxyContin® URDD Rates per 1,000

**Poison Center**

<table>
<thead>
<tr>
<th></th>
<th>2008Q4</th>
<th>2009Q2</th>
<th>2009Q4</th>
<th>2010Q2</th>
<th>2010Q4</th>
<th>2011Q2</th>
<th>2011Q4</th>
<th>2012Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/1000 URDD</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Drug Diversion**

<table>
<thead>
<tr>
<th></th>
<th>2008Q4</th>
<th>2009Q2</th>
<th>2009Q4</th>
<th>2010Q2</th>
<th>2010Q4</th>
<th>2011Q2</th>
<th>2011Q4</th>
<th>2012Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/1000 URDD</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Drug**

<table>
<thead>
<tr>
<th></th>
<th>Oxycontin</th>
<th>Other Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ(%)</td>
<td>-31.3%</td>
<td>-10.0%</td>
</tr>
</tbody>
</table>

**Drug**

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

URDD: Unique recipients of dispensed drug
OxyContin® URDD Rates per 1,000

**Opioid Treatment Program**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Δ(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycontin</td>
<td>-14.8%</td>
</tr>
<tr>
<td>Other Opioids</td>
<td>-11.6%</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
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

• Reformulated OxyContin may be abuse deterrent for opioids in general

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

URDD: Unique recipients of dispensed drug; SKIP: Survey of key informants’ patients
Hydromorphone (Class)
URDD Rates per 1,000

**Poison Center**

- Exposures/1000 URDD

- Pre-Exalgo
- Post-Exalgo

**Drug Diversion**

- Cases/1000 URDD

URDD: Unique recipients of dispensed drug
Hydromorphone (Class)  
URDD Rates per 1,000

**Opioid Treatment Program**

**Survey of Key Informant Patients**

URDD: Unique recipients of dispensed drug
Exalgo / Hydromorphone Conclusions

• Hydromorphone misuse, abuse and diversion rates per population and URDD have been increasing over time

• Release of Exalgo in March 2010 corresponded with changes in these trends
  – Post-Exalgo release trends declining or remaining stable
  – Decreasing trends in abuse among high risk populations (OTP) were statistically significant after release

• Further study of overall changes in trend patterns continue in RADARS System

URDD: Unique recipients of dispensed drug; OTP: Opioid treatment program
Availability of Buprenorphine has Expanded
Unique Recipient of Dispensed Drug (URDD)

URDD: Unique recipients of dispensed drug
Opioid Treatment Program
URDD Rate 2010 Q1 - 2012 Q1
Survey Key Informants' Patients
URDD Rate, 2010 Q1 – 2012 Q1

Endorsements/1000 URDD

- Total buprenorphine
- SI buprenorphine tablets
- Suboxone® tablets
- Suboxone® oral film
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
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).

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>Age, y</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>
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<tr>
<td>Outcome, No. (%)</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>
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<tr>
<td>Death</td>
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<td>0</td>
<td>2 (0.7)</td>
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<td>4 (0.3)</td>
<td>8 (0.1)</td>
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<td>136</td>
<td>779</td>
<td>3,540</td>
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<tr>
<td>Confirmed</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>

*nonexposure
Moving Forward: USA

• Pharmaceutical strategies
  – Improve physical tamper resistance (i.e. OxyContin®, Exalgo®)
  – Decrease abuse potential chemically (i.e. Suboxone®)

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

• Measuring impact of these strategies
  – RADARS® System Data Trending
  – Mosaic approach
Poison Center Studies

• Global Poison Center Collaboration
  – Harmonization of poison center data from 7 countries from 2007 through 2010
    • United States, United Kingdom, Germany, Italy, Netherlands, Switzerland, Australia

• Objective
  – Characterize human exposures to prescription opioids and stimulants reported to poison centres
Opioid Treatment Studies

• European Opiate Addiction Treatment Association (Europad) Pilot
• Principal Investigator: Icro Maremmani
  – Currently collecting data from opioid treatment facilities in 4 countries
    • Italy, Spain, France, and Germany
  – Data collection to continue through the spring 2013
  – Minimum of 250 surveys from each country
Future Plans

• Expansion of surveillance of EU opioid treatment programs
Lessons Learned

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

• Abuse deterrent of tamper resistant formulations can impact misuse and diversion of prescription opioids
  – Dependent upon how drug is misused
  – Important to monitor consequence of “squeezing the balloon”

• Systematic measurement to gauge impact of interventions is critical
  – Baseline data to understand trends
  – Consistent methodology
Thank You!

For further information or questions:

jody.green@rmpdc.org

www.radars.org
Q&A SESSION

PROFESSOR ICRO MAREMMAN
University of Pisa, Italy
TRENDS OF OPIOID MISUSE AND DIVERSION: LESSONS FOR EUROPE FROM THE USA

DR JODY GREEN
Rocky Mountain Poison and Drug Center, USA

PROFESSOR ICRO MAREMMANI
University of Pisa, Italy