Research Design Considerations for Clinical Studies of Abuse Deterrent Opioid Analgesics

Poison Center Data to Assess the Relative Abuse Rates of Prescription Opioids

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Goal: Minimize abuse and diversion (MAD) while providing pain control for patients.

A claim of decreased abuse is difficult to study
- Behaviors to be measured are illegal, heavily stigmatized, and concealed.

Use systems to measure when the subject is “forced” to expose themselves (the “mosaic” approach).

Conclusions may vary depending on measure
Relative Abuse Rates of Prescription Opioids

- Is the new drug abused?
- How does the abuse compare to other drugs?
  - Importance of denominators
- Who abuses the product?
- How is the new product being abused?
  - Ingestion, Inhalation (snorting), Injection, other
- Are there unintended victims?
- How will the information be applied?
  - To assess abuse resistance/deterrence?
RADARS® System Mosaic

Prescription Medication Issues
- Hidden events & motives
- Indications
- Formulations
POISON CENTERS
1-800-222-1222 Nationwide

- Poison Center.
- Poison Center that serves other States.
- State that does not have a Poison Center and is served by another State.

Refer to the information below for detailed coverage information.
- 85% Home
- 15% Health care

- All States
- Public Health Depts
- Chemical Mfrs
- Consumer Product Mfrs
- Pharmaceutical Mfrs
- Petroleum Industry
- Retail Industry

Nationally Standardized Data Collection System
2.5 million exposures 2007
Medical Advice

- Triage and care advice
  - 800-222-1222, 24 x 7 x 365

- National standards
  - Certified staff
  - Accredited centers

- Prehospital guidelines

- Board certified physician backup
Data Collection

- All centers report data to National Poison Data System (NPDS) every 14 minutes
- Standardized data fields
  - Explicit definitions
    - Demographics
    - Substance information
    - Exposure information
    - Clinical effects
    - Therapy
    - Outcomes

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NPDS Classification System

Calls to Poison Centers 2008

Exposure Call

- Intentional
  - Suicide 208,442
  - Abuse 45,796
  - Misuse 51,677
  - Intent. Unk 17,452

- Unintentional

Information Call

- Pill ID
  - Drug Info
  - Other

Strengths of Data Collection

- Standardized data collection
- Health care professionals (RN, PharmD)
  - National certification exam
- Entire US population has access
  - Marketing to promote use
  - Toll free number - 24/7/365
  - Real time data collection
- Product specificity
- Geographic specificity (3DZ)
- Quality assurance
  - Fields have rules
Weaknesses of Data Collection

- Spontaneous reporting
  - PCs required to maintain call volume from all 3 DZ in their area
- Quality assurance
- Omissions
- Clinical judgments are recorded
- Case notes are not available
Can Poison Centers Detect Introduction of New Drug?

Rate per 100,000 Population

YearQuarter

Rate per 100,000 Population

-0.01

0.01

0.19

0.39

0.59

0.79

0.99

20031

20032

20033

20034

20041

20042

20043

20044

20051

20052

20053

20054

20061

20062

20063

20064

20071

20072

20073

20074

20081

20082

20083

20084

New Drug

Total

ID/Info

Total Exposures

Intentional Exposures

Unintentional/Other Exposures
Can Poison Center Data Detect Changes?

Unlawful Narcotics Investigations, Treatment and Education

www.operationunite.org
UNITE Background

• First activities early 2004 - 29 counties in Eastern Kentucky

• Methods
  • Undercover narcotics investigations
  • Treatment for substance abusers 1-866-90-UNITE
  • Provides support to families and friends of abusers
  • Educates the public about the dangers of using drugs
Drug Roundups
On April 6, 2004, Operation UNITE conducted a roundup of 210 suspected drug dealers in the eight-county Kentucky River area – the largest such operation in Kentucky’s history. The sweep involved numerous city, county and state law enforcement agencies.

Through December 30, 2008, there have been 120 roundups, with at least one in each of the 29 counties in the Fifth Congressional District.
Applying PC Data to a Abuse Resistant Product
Yes, new product is abused

Rate per 100,000 population

Rate per 1000 URDD
How Does Abuse Compare to Other Opioids?

Poison Center Intentional Exposures

Rate per 100,000 population

YearQuarter

Rate per 100,000 Population

New Drug
Fentanyl
Hydromorphone
Hydrocodone
How Does Abuse Compare to Other Opioids?
Poison Center Intentional Exposures
Rate per 1,000 URDD

New Drug
Fentanyl
Hydromorphone
Hydrocodone
Intentional abuse: Intentional improper or incorrect use of a substance … likely attempting to achieve a euphoric or psychotropic effect. All recreational use is included.
How Does Abuse Compare to Other Opioids?

Associated Medical Outcome
Percent of Intentional Exposures, 2003-2008
Route of Administration

- Many opioid medications are abused by a non-oral route of administration
- Route of administration data is provided by four RADARS System programs
  - Survey of Key Informant Patients (SKIP)
  - College Student Survey
  - Poison Centers
  - Opioid Treatment Programs
Does Tampering Occur?
Route of Administration, RADARS® System Poison Centers

![Bar chart showing the percent of abuse cases by route of administration. The routes include Ingestion, Parenteral, Inhalation, Ingestion & Inhalation, Ingestion & Parenteral, and Unknown. The bar for Ingestion is the highest, followed by Parenteral, Inhalation, and the others being much lower. The chart highlights a new drug.](image-url)
### College Survey, 1Q 2009
### Routes of Administration

<table>
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<tr>
<th>Drug</th>
<th>N</th>
<th>Swallow %</th>
<th>Chewed %</th>
<th>Inhaled %</th>
<th>Inject %</th>
<th>Derm %</th>
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<tbody>
<tr>
<td>New Drug</td>
<td>20</td>
<td>55.0</td>
<td>40.0</td>
<td>40.0</td>
<td>10.0</td>
<td>0</td>
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<td>Fentanyl</td>
<td>22</td>
<td>22.7</td>
<td>63.6</td>
<td>27.3</td>
<td>4.6</td>
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<td>Hydrocodone</td>
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<td>16.6</td>
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<td>Hydromorph.</td>
<td>24</td>
<td>62.5</td>
<td>33.3</td>
<td>25.0</td>
<td>12.5</td>
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<td>Methadone</td>
<td>23</td>
<td>73.9</td>
<td>39.1</td>
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<td>Morphine</td>
<td>29</td>
<td>58.6</td>
<td>34.5</td>
<td>20.7</td>
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<td>Oxycodone</td>
<td>103</td>
<td>79.6</td>
<td>23.3</td>
<td>25.2</td>
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<td>Stimulants</td>
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<td>85.8</td>
<td>21.1</td>
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<td>95.8</td>
<td>16.7</td>
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1. Per caller: Person I know is crushing up New Drug, warming it in spoon and shooting up with it. He is acting really agitated, shaking and really hyperactive. What should I do?

2. S; Dr want PC opinion... 53 y/o F took ?? amts of fentanyl and morphine that was for son's PCA pump for pain (son has cancer) and injected self IV. EMS found unresponsive with resp 6, IV, naloxone admin, pt AAO x 3 on arrival
How is the Product Abused?
RADARS® System Poison Centers, Rates for all centers

- Caller: sister is a heroin addict and she is prescribed with generic hydrocodone/apap and she grabbed a tablet scraped it and added water and shoot it up. She is currently asx. caller wants to know what to do.
- ER: have adult female that scraped and injected a fentanyl patch. Unk concentration..Came into ER lethargic and hypoventilating. Narcan and woke up.
- EMS call: medics on scene w/ 17 yo that supposedly injected XX oxycodone 3-4 hrs ago and has taken a few Oxycodone/Apap throughout the day. Currently awake and alert. Medics see some kind of trigeminy on the monitor. PCC rec transport.
Are There Vulnerable Populations?

  - 2003-2006
  - Any call for a child < 6 years and 1 opioid drug
    - Buprenorphine
    - Fentanyl
    - Hydrocodone
    - Hydromorphone
    - Methadone
    - Oxycodone
    - Oxymorphone
    - Tramadol
Pediatric Opioid Exposures

Results

- 9,240 exposure mentions involving 9,179 children. National - at least two fold higher
  - Age range newborn to 5.5 years
  - Ingestion (99%), unintentional (>99%)
  - 92% occurred in the child’s home (92%)
  - 8 deaths
- National 2006 AAPCC data – 9 of 29 (31%) deaths in child < 6 yrs 9 deaths were associated with an opioid drug
**New Drug: Children are Affected**

**Poison Center Unintentional Exposures, 2003 – 2008**

- **<6 Years**
  - High exposure.
  - No deaths.

- **6-12 Years**
  - Low exposure.
  - No deaths.

- **13-19 Years**
  - Low exposure.
  - No deaths.

- **20-29 Years**
  - Low exposure.
  - No deaths.

- **30-39 Years**
  - Low exposure.
  - No deaths.

- **40-49 Years**
  - Low exposure.
  - No deaths.

- **50-59 Years**
  - Low exposure.
  - No deaths.

- **>59 Years**
  - Low exposure.
  - No deaths.

- **Unk**
  - Primarily mixed drug deaths.
Recommendations - 1

- Surveillance must play a role in evaluating abuse deterrence/resistance.
- Some firm decisions or foundational concepts should be developed now.
- A claim for abuse resistance should be limited to a specific context.
  - i.e. reducing experimental abuse in young adults
- Other surveillance systems should be developed to assess potential claims
We need to compare total abuse among drugs.

Selection of comparator drug could depend on specific label. For example, if the abuse resistant drug is an controlled release product intended to treat chronic pain, it could be compared to OxyContin.

Mosaic approach

- At least 3 populations should be included: Abusers, Children, Experimenters
- Comparison to at least two other drugs – label and actual use

Since time plays a role, needs to be ongoing.
THE END