Diversion, Abuse, and Pediatric Exposures to Sublingual Buprenorphine Products

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Buprenorphine/Naloxone Abuse and Diversion: Film Rates are Less Than Tablet Rates
Green JL, Martinez EH, Severtson SG, Cicero TJ, Kurtz SP, Rosenblum A, Surratt HL, Dart RC, Lavonas EJ

Buprenorphine/Naloxone Pediatric Ingestion: Exposure Rates Differ Between Film and Tablet Formulations
Green JL, Martinez EH, Severtson SG, Dart RC, Lavonas EJ
Research Funding

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- RMPDC operates the RADARS® System
  - Overseen by independent Scientific Advisory Board
  - Supported by subscription fees from industry
  - Provides data for the buprenorphine shared REMS (jointly funded by RBP and its competitors)
Other Disclosures

• Earlier versions of these data have been published
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  • *J Subst Abuse Treat* 2014, *in press.*
• Trade names used only when needed for clarity
• No discussion of off-label use
Overview

• Sublingual buprenorphine
• The RADARS System
• Diversion and abuse rates
• Pediatric exposure rates
Buprenorphine

• High affinity $\mu$-opioid partial agonist
• Treatment of pain
  • Transdermal (Butrans®)
  • Oral (Temgesic®) (ex-US)
• Treatment of opioid addiction
  • Sublingual formulations
Sublingual Buprenorphine

- Introduced in the US in 2002
- Indication: Treatment of opioid addiction in adults
- Requires special DEA endorsement to prescribe
  - Mandatory training
  - Limit of 200 patients per provider (up from 30)
- First-line therapy for opioid addiction
  - Management of acute withdrawal
  - Stabilization
Sublingual Buprenorphine

• Buprenorphine tablets
  • Subutex® → generics

• Buprenorphine/naloxone tablets
  • Suboxone® → generics

• Buprenorphine/naloxone film
  • Suboxone®
Sublingual Buprenorphine
The RADARS® System

- Founded in 2001 by Purdue Pharma
- Since 2006, operated by the Rocky Mountain Poison and Drug Center
  - Division of the Denver Health and Hospital Authority
- Independent Scientific Advisory Board
The RADARS® System

• Collects product-specific data
  • More than 120 different products
    • Opioids
    • Stimulants
• Quarterly data collection
• Rigorous QA process
• Unit of analysis based on project need

<table>
<thead>
<tr>
<th>Level</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Suboxone® sublingual tablets</td>
</tr>
<tr>
<td>Formulation</td>
<td>Buprenorphine/naloxone tablets</td>
</tr>
<tr>
<td>Active Pharmaceutical Ingredient</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Class</td>
<td>Opioids</td>
</tr>
</tbody>
</table>
RADARS® System Mosaic Approach

Poison Center
- Acute Events
  - 48 centers
  - 46 states

Opioid Treatment (OTP)
- Patients in Tx
  - 73 programs
  - 33 states

College Survey
- 2000 students
  - 50 states
  - 3x each year

Drug Diversion
- Law Enforcement
  - 250 investigators
  - 50 states

Survey of Key Informant Patients (SKIP)
- Patients in Tx
  - 125 practices
  - 50 states

StreetRX (website)
- User/Buyers Crowdsourcing
  - 50 states

Web Monitoring
QA: Buprenorphine Coding

**Initial Coding Counts**
- Suboxone Oral Film: 693
- Suboxone Tablets: 395

**Final Coding Counts**
- Suboxone Tablets: 390
- Suboxone Oral Film: 303
- Suboxone Tablets: 379
- Suboxone Oral Film: 16

Research Question

• Do the program event ratios (rates) of diversion, abuse, and pediatric exposures differ between the three buprenorphine sublingual formulations?
Program Events

- Drug Diversion Program
  - New law enforcement investigations
- Treatment Programs
  - Used in the past 30 days “to get high”
- Poison Center Program
  - Can study any category of exposure
  - For this report:
    - Reason = Unintentional
    - Age ≤ 5 years
Denominators

• Population
  • Estimates overall public health burden

• Drug availability
  • Patients filling prescriptions
    • “Unique recipients of a dispensed drug”, URDD
  • Estimates risk to an individual
  • Compensates for changes in prescribing practice
  • Informs policy changes that might affect utilization
Changes in Buprenorphine Prescribing

<table>
<thead>
<tr>
<th>Year / Quarter</th>
<th>URDD per 10,000 Population</th>
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</thead>
<tbody>
<tr>
<td>2010/4</td>
<td>2</td>
</tr>
<tr>
<td>2011/1</td>
<td>8</td>
</tr>
<tr>
<td>2011/2</td>
<td>6</td>
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<tr>
<td>2011/3</td>
<td>4</td>
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<tr>
<td>2012/1</td>
<td>12</td>
</tr>
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<td>2012/2</td>
<td>10</td>
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<tr>
<td>2012/3</td>
<td>8</td>
</tr>
<tr>
<td>2012/4</td>
<td>6</td>
</tr>
</tbody>
</table>

- **Red**: Buprenorphine tablets
- **Blue**: Buprenorphine / naloxone tablets
- **Green**: Buprenorphine / naloxone film
Calculations

- Program events per 10,000 URDD
- Calculated quarterly
- First combination film data in program → 2013 Q1
- Averages and 95% CIs calculated using negative binomial regression
Drug Diversion Investigations

![Graph showing the number of diversion events per 10,000 URDD over time, with lines distinguishing between combination tablets, single ingredient tablets, and combination film. The x-axis represents quarters from 2009Q4 to 2013Q1, and the y-axis shows the number of diversion events per 10,000 URDD.]
## Drug Diversion Investigations

<table>
<thead>
<tr>
<th></th>
<th>Rate Investigations per 10,000 URDD</th>
<th>95% CI</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Ingredient Tablets</td>
<td>8.7</td>
<td>7.6 – 9.8</td>
<td>6.7</td>
<td>5.5 – 8.2</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Combination Tablets</td>
<td>13.6</td>
<td>12.8 – 14.5</td>
<td>10.6</td>
<td>9.0 – 12.4</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Combination Film</td>
<td>1.3</td>
<td>1.1 – 1.5</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calculations based on 1,505 reports of buprenorphine diversion, October 2010 – March 2013
Abuse Endorsements

Abuse Cases per 10,000 URDD

- Suboxone Sublingual Tablets
- Buprenorphine Monoingredient Tablets
- Suboxone Sublingual Film

Single ingredient tablets
Combination tablets
Combination film

RADARS SYSTEM
# Abuse Endorsements

<table>
<thead>
<tr>
<th></th>
<th>Rate Endorsements per 10,000 URDD</th>
<th>95% CI</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Ingredient Tablets</td>
<td>61.8</td>
<td>59.2 – 64.6</td>
<td>6.8</td>
<td>6.3 – 7.3</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Combination Tablets</td>
<td>21.3</td>
<td>20.3 – 22.3</td>
<td>2.3</td>
<td>2.2 – 2.5</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Combination Film</td>
<td>9.1</td>
<td>8.7 – 9.6</td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
</tbody>
</table>

Calculations based on 5,293 reports of buprenorphine abuse, April 2011 – March 2013
Young Child Exposures

Pediatric Exposure Cases per 10,000 URDD

- Suboxone Sublingual Tablets
- Buprenorphine Mono-Ingredient Tablets
- Suboxone Sublingual Film

Combination tablets
Single ingredient tablets
Combination film
# Young Child Exposures

<table>
<thead>
<tr>
<th></th>
<th>Rate Exposures per 10,000 URDD</th>
<th>95% CI</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Ingredient Tablets</td>
<td>2.8</td>
<td>2.4 – 3.2</td>
<td>3.1</td>
<td>2.6 – 3.7</td>
<td>P &lt; 0.0001</td>
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<tr>
<td>Combination Tablets</td>
<td>7.0</td>
<td>6.6 – 7.3</td>
<td>7.6</td>
<td>6.7 – 8.6</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Combination Film</td>
<td>0.9</td>
<td>0.8 – 1.0</td>
<td>Reference</td>
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</table>

Calculations based on 1,695 reports of exposures to buprenorphine, January 2011 – March 2013
What Does This Mean?

• Drug diversion investigations
  • Highest for combination tablets
  • Lowest for film
• Abuse by patients entering treatment
  • Highest for single-ingredient tablets
  • Lowest for film
• Young child exposures
  • Highest for combination tablets
  • Lowest for film
Potential Causes for Diversion / Abuse Differences

• Naloxone is bio-available by injecting/snorting
  • Abuse-deterrent

• No explanation why diversion rates for combination tablets exceed single ingredient tablet rates
  • Internet monitoring: tablets produce better “high” than film
Potential Causes for Pediatric Exposure Differences

• Formulation
• Packaging
• Carry-over from abuse distribution
Limitations

• Misclassification of substance
• Differential reporting
• Are different formulations prescribed to different populations?
• Choice of denominator: patients vs. unit doses