Post-Marketing Surveillance of Controlled Substance Abuse and the Emergence of REMS

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SEPTEMBER 24 & 25, 2009
What are REMS?

- **Risk Evaluation and Mitigation Strategies**

- The FDA now mandates that a new opioid analgesic must have a program to:
  - Identify, localize and characterize abuse and diversion, and other adverse events with newly marketed drugs.
  - Once this information is in hand, develop a plan to “mitigate” the abuse.
Why are REMS Needed?

- Phase I-III studies tend to be small relative to general population so that relatively rare events will be missed or underestimated.

- Data over the past decade indicates a sharp increase in Rx abuse and diversion.
Why has Rx abuse increased so markedly in the past decade?
Why has Rx Abuse Increased?

- Arguably, errors in the labeling of OxyContin and the enormous quantity of drug in a single tablet led to its widespread abuse.

- Rx drugs are considered legal and therefore it is believed there are no penalties for usage.

- Taking them is safe because of authenticity and dose certainty.
Why has Rx Abuse Increased?

- Easily available from doctors, friends and/or family.
- No perceived stigma associated with use.
- Don’t consider themselves addicts.
The RADARS™ System is composed of five signal detection systems:

- Drug Diversion
- Survey of Key Informants’ Patients (SKIP)
- Poison Center
- Opioid Treatment Program
- College Survey
Key Informants are experts in the field of substance abuse and pain medicine, most often treatment center directors.
Survey of Key Informant Patients (SKIP)

- Questionnaire, self-addressed envelope and gift card are sent to Key Informants.
  - Key Informants have their patients/clients complete questionnaires which carry a specific ID #.

- Questionnaire returned directly to Washington University (treatment center does NOT see completed survey)
  - Key Informants are notified that a questionnaire has been completed.
  - Patient receives gift card for participation
Characteristics and Patterns of Abuse
What Drugs are Used Most Frequently?

Drugs Used in the Past 30 Days Among Rx Abusers per Quarter 20081 - 20093

- Buprenorphine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Tramadol
SKIP Oxycodone Abuse Rate (per 100,000 pop) for 2008
SKIP Hydrocodone Abuse Rate (per 100,000 pop) for 2008
Methadone SKIP Abuse Rate (per 100,000 pop) for 2008
What drugs are used most frequently?
What Drugs are Used Most Frequently?

Drugs Used in the Past 30 Days Among Rx Abusers
2007 - 2009
What Drugs are Used Most Frequently?

Primary Drugs Among Rx Abusers, 2007-2009
What Drugs are Used Most Frequently?

Source of Primary Drug in the Past 30 Days Among Rx Abusers, 2007 - 2009
What Drugs are Used Most Frequently?

Route of Primary Drug Administration in the Past 30 Days Among Rx Abusers, 2007 - 2009
But abuse is a little more complicated than that...
But abuse is a little more complicated...

Drugs Used in the Past 30 Days Among Rx Abusers
2007 - 2009

- Buprenorphine
- Fentanyl
- Heroin
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Tramadol
But abuse is a little more complicated...

### Primary Drug vs. Preferred Drug Among Rx Abusers if Price and Availability Were Not Factors, 2007-2009

- **Primary Drug**
- **Preferred Drug**
Is the recent surge in Rx abuse a new problem in otherwise healthy individuals?
<table>
<thead>
<tr>
<th><strong>SKIP: Rx Abusers (N=2020)</strong></th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>- Males (49.9%)</td>
</tr>
<tr>
<td>- Females (50.1%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
</tr>
<tr>
<td>- None (10.79%)</td>
</tr>
<tr>
<td>- High School/GED (42.75%)</td>
</tr>
<tr>
<td>- Some College (46.46%)</td>
</tr>
<tr>
<td><strong>Average Age:</strong> 35.03</td>
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<tr>
<td><strong>Ethnicity</strong></td>
</tr>
<tr>
<td>- White (82.48%)</td>
</tr>
<tr>
<td>- African-American (5.29%)</td>
</tr>
<tr>
<td>- Latino/a (4.29%)</td>
</tr>
<tr>
<td>- Other (7.94%)</td>
</tr>
</tbody>
</table>
Avg. # of times entered drug treatment: 3.5

Reported Chronic Pain: 59.8%

Avg. 1-10 Pain Score: 4.9

Treated for Psychiatric Condition: 44.3%
Nicotine Dependence: 67.3%

Alcohol Abuse: 40.3%

Meet DSM-IV Criteria for Abuse of Primary Rx: 89.8%
SF-36v2 Results of Male vs. Female Rx Abusers

Male Rx Abusers
Female Rx Abusers
National Norm Males
National Norm Females
Why is Co-morbidity a Problem?

- Treatment requires a multi-discipline approach.
- Treating Rx abuse in isolation is destined to fail.
Why is Co-morbidity a Problem for REMS?

- What does a REMS target as a mitigation strategy?
More Difficulties in Implementing REMS

- Identifying abuse is not a problem.

- Doing something about it is a laudable, but perhaps unattainable goal.

- Why?
  - Unless you have good data beforehand (i.e., no REMS) how can you assess whether the minimization approach was successful?
  - Given regional localization of abuse, national databases will not likely be very helpful.
More Difficulties in Implementing REMS

- Why? (cont’d)
  - Abuse in some areas (e.g., Appalachia) has been indigenous for decades. What can be done to eradicate abuse of a new drug within this culture.
  - Balloon analogy.
Unintended Consequences

- Will REMS for a specific drug be so restrictive that patients – not just addicts – will be denied beneficial medications?