The Epidemiology of Prescription Opioid Abuse: A Regulatory Perspective

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Role of the Drug Regulator

- Access to medicines
  - Assess efficacy, safety, quality
- Protection of the public
  - During clinical trials
  - Postapproval
- Information to the public
An Important Public Health Problem

**Figure 20. Past Year Opioid Misuse among People Aged 12 or Older: 2017**

- 11.1 Million People with Past Year Pain Reliever Misuse (97.2% of Opioid Misusers)
- 562,000 People with Past Year Pain Reliever Misuse and Heroin Use (4.9% of Opioid Misusers)
- 886,000 People with Past Year Heroin Use (7.8% of Opioid Misusers)
- 10.5 Million People with Pain Reliever Misuse Only (92.2% of Opioid Misusers)
- 324,000 People with Heroin Use Only (2.8% of Opioid Misusers)

11.4 Million People Aged 12 or Older with Past Year Opioid Misuse

Note: Opioid misuse is defined as heroin use or prescription pain reliever misuse.

**Figure 38. Opioid Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: 2017**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of People (in Thousands)</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>12 or Older</td>
<td>2,110</td>
<td>1.3</td>
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<tr>
<td>12 to 17</td>
<td>103</td>
<td>0.8</td>
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<tr>
<td>18 to 25</td>
<td>445</td>
<td>1.3</td>
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<tr>
<td>26 or Older</td>
<td>1,562</td>
<td>0.7</td>
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Note: Opioid use disorder is defined as meeting DSM-IV criteria for heroin use disorder or pain reliever use disorder in the past 12 months.

Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics Products from U.S. Outpatient Retail Pharmacies

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products
Considering public health impact in opioid drug approvals

- From NASEM:
  - “Integrating public health considerations into [FDA’s] regulation of opioids—including its approval decisions on new opioids—would be consistent with both its past practice and a generally accepted understanding of its statutory authority.”
  
  - “Public health considerations may include how the availability or use of the product will affect an unintended population or the broad public health impact resulting from the aggregated effects on patients taking the drug.”
The Opioid Epidemic and Pharmacoepidemiology

• A societal problem
• Misuse, abuse, addiction, overdose and death are safety issues
• Involves both patients to whom an opioid was prescribed and non-patients
• Difficult to study and quantify
Pathways to Abuse/Misuse of Prescription Drugs and Related Adverse Outcomes

Drug diversion

Drug manufactured
Drug distributed
Drug prescribed/dispensed

Patient supply

Patient use as prescribed

Abuse
Misuse
Addiction
Overdose
Death

Inappropriate use by patients

Population Surveys (self-report)
Health Care Utilization data

Outcome captured in...

Nationally-representative household and school surveys
Treatment center surveys
Internet surveys
Poison Center data
Emergency Department Visit and Hospitalization data (claims, EMR)
Addiction treatment admissions
National Vital Statistics, linked death registry data
Medical Examiner data (limited availability)
National death certificate literal text (in development)
No Single Data Source Provides the Whole Picture

Healthcare Utilization Data
- Poison Control Calls
  - Calling for advice on drug exposures; captures unknown spectrum of problems
- ED Visits/Hospital Admissions
  - Seeking medical treatment - possibly incidental finding related to overdose/infection; captures unknown spectrum of problems

Surveys
- National Health/School Surveys
  - National samples; eligibility/sampling may capture less-severe problems
- Internet Surveys
  - Belong to internet panel; may capture less-severe problems
- Treatment Center Surveys
  - Getting/being assessed for SUD/addiction treatment; captures more severe problems
- Addiction Treatment Admissions

All opioid misuse, abuse, addiction

ED, emergency department; SUD, substance use disorder
Postmarket Safety - What We Want to Learn

- Learn about new risks
- Learn more about known risks
- Learn about medication errors
- Learn about product defects
- Learn how patterns of use may contribute to unsafe use
- Learn about the impact of our interventions
Learning about New Risks – OTC Loperamide Abuse

• Approved in 1976
• Safe and effective for diarrhea when used as directed
• Signal of cardiotoxicity detected in FDA’s Adverse Event Reporting System (FAERS)
  – 48 cases of serious cardiac disorders associated with loperamide more than half since 2010
  – Cases were associated with doses much higher than recommended or with interacting medicines that resulted in high loperamide levels
  – Cases reported syncope, cardiac arrest, QT interval prolongation, ventricular tachycardia, and Torsade de Pointes
  – Ten cases resulted in death
FDA Actions on Loperamide

June 7, 2016
Risk of serious heart problems that can lead to death with higher than recommended doses

January 30, 2018
Oral solid packages sizes limited to 48 mg

Stakeholder engagement
Learn More about Known Risks – Rescheduling of Hydrocodone

• Hydrocodone
  – Abuse potential was already known
  – Wide availability created public health problem

• Controlled Substances Act had placed hydrocodone in two different Schedules in the CSA:
  – Schedule II
    • Hydrocodone substance
  – Schedule III
    • Hydrocodone (in specified amounts) in combination with an isoquiline alkaloid of opium (specified amounts), or
    • Hydrocodone (in specified amounts) in combination with one or more therapeutically active non-narcotic ingredients
Learn More about Known Risks – Rescheduling of Hydrocodone

DAWN Data Analyzed with Various Denominators – 2007

Denominator = US Population

Denominator = 100 Kgs Sold

Denominator = Million Tablets Dispensed

*OSE Analysis. Sources: Center for Behavioral Health Statistics and Quality, SAMHSA; IMS Health, Vector One®: National (VONA). Extracted 9/08

Re-scheduling of Hydrocodone

– C-III to more restrictive C-II (October 2014)
– FDA evaluation of impact on use and abuse is ongoing
– Hard to isolate effect of rescheduling, in light of all the other programs happening at same time
Dispensed Prescriptions Containing Hydrocodone from U.S. Outpatient Retail Pharmacies Have declined Since Rescheduling*

*IQVIA prescription data, 2016
Rates of Abuse Calls* and Deaths** Involving Select Opioid Analgesics and Heroin

* American Association of Poison Control Centers data, 2016

**Drug Involved Mortality data, 2015 (National Center for Health Statistics)
Learning More About Known Risks – Postmarketing Requirements for ER/LA Opioid Analgesics

Long-term Therapeutic Use of Prescription Opioid Analgesics

What is this rate and what are its determinants?

Baseline Characteristics
- Indication for use
- Pain intensity
- Prior opioid use
- Other comorbidities
- Other factors

Time-varying factors
- Disease course
- Treatment response
- Dose changes
- Other factors

Addiction and Other Adverse Consequences

Outcome Ascertainment
- What to measure
- Validity of measures
- Completeness of capture
Postmarketing Requirements for ER/LA Opioid Analgesics

• Ten observational studies
  – 8 of 10 study reports are under review
  – 2 main studies to estimate incidence of adverse effects are still underway
• One clinical trial
  – Still underway

“Recognizing that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids, the FDA is requiring the drug companies that make these products to conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death.”
Learning About Medication Errors - Accidental Exposures of Children to Fentanyl Patches

- Thirty cases of pediatric accidental exposure identified
  - Serious harm
    - Death (n=10)
    - Hospitalization and medical intervention (n=16).
    - Age of the child <10 years (n=28)
      - Age 2 years or younger (n=19)
FDA Actions on Fentanyl Patches

September 23, 2012
Change in color of patch

September 23, 2013
Fentanyl Patch Can Be Deadly to Children

FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) pain patches to aid safety—emphasizing that accidental exposure to used patches can cause death

Communication
Learning about Product Defects - Opana ER

• Postmarketing data suggested that reformulation of Opana ER (never labeled with abuse-deterrent properties)
  – Decreased nasal abuse, BUT
  – Caused a shift among abusers to more dangerous route, from snorting to injecting—unintended consequence
    – Seen in both poison control center and treatment center data
    – Consistent with spontaneous report patterns and information from outbreak investigations
    – Geographic clustering
Tampering practices

HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015

New inactive ingredient – polyethylene oxide

FDA Actions on Opana ER

March 13-14, 2017
Advisory Committee votes 8-18 that the benefits of reformulated Opana ER do not outweigh the risks.

June 8, 2017

FDA requests removal of Opana ER for risks related to abuse.
Learning About How Patterns of Use May Contribute to Unsafe Use – Opioid and Benzodiazepine Use

41% relative increase in co-prescribing

Table 2. Proportion of Opioid Recipients With Concomitant Benzodiazepine Use, 2002–2014 (n=177 million)

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<tbody>
<tr>
<td>All opioid recipients</td>
<td>6.6</td>
<td>6.6</td>
<td>6.8</td>
<td>7.3</td>
<td>7.6</td>
<td>8.2</td>
<td>8.6</td>
<td>8.5</td>
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<tr>
<td>Male</td>
<td>5.5</td>
<td>5.2</td>
<td>5.4</td>
<td>5.8</td>
<td>6.1</td>
<td>6.7</td>
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<tr>
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<tr>
<td>0–17 years</td>
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<tr>
<td>18–44 years</td>
<td>4.5</td>
<td>4.4</td>
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<td>6.0</td>
<td>6.4</td>
<td>6.1</td>
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<td>5.5</td>
<td>6.4</td>
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<td>45–64 years</td>
<td>8.8</td>
<td>8.4</td>
<td>8.7</td>
<td>9.2</td>
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<td>65+ years</td>
<td>11.1</td>
<td>10.5</td>
<td>10.5</td>
<td>10.7</td>
<td>10.9</td>
<td>11.4</td>
<td>11.6</td>
<td>11.6</td>
<td>11.6</td>
<td>11.6</td>
<td>11.6</td>
<td>12.0</td>
<td>12.0</td>
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<tr>
<td>Chronic users</td>
<td>41.4</td>
<td>39.1</td>
<td>39.3</td>
<td>39.5</td>
<td>37.2</td>
<td>37.8</td>
<td>37.7</td>
<td>40.5</td>
<td>40.3</td>
<td>39.7</td>
<td>38.0</td>
<td>35.5</td>
<td>33.9</td>
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<tr>
<td>Nonchronic users</td>
<td>3.6</td>
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<td>3.5</td>
<td>3.6</td>
<td>3.7</td>
<td>4.3</td>
<td>4.3</td>
<td>4.1</td>
<td>4.2</td>
<td>4.2</td>
<td>4.3</td>
<td>4.4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Note: Values are percentages.
*Patients were considered concomitant users if they had one or more opioid and benzodiazepine episodes that overlapped by 7 or more consecutive days.
*Percent of concomitant patients, out of the total number of opioid recipients during a given calendar year.
*Patients with at least one opioid episode ≥90 days during the study period were considered chronic opioid users. All other patients were considered non-chronic opioid users. For chronic opioid users, concomitancy proportions were based on opioid episodes ≥90 days only.

Opioids and Benzodiazepines - Overdose Deaths

Figure 5 Incidence rate ratios for overdose deaths involving opioid analgesics, by benzodiazepine prescription status. ... Unadjusted death rates for drug overdose by benzodiazepine prescription history and daily opioid dose. Error bars represent 95% confidence intervals. Unadjusted overdose death rates are estimates for entire source population.

Population-based cohort study of all North Carolina residents alive in 2010.

Case-cohort study among US veterans.

FDA Actions on Opioid-Benzodiazepine Co-Prescribing

August 31, 2016
Announces Boxed Warning about the risks of concomitant use of opioids and benzodiazepines

September 26, 2017
Refines message regarding buprenorphine and methadone
Learning About the Impact of Our Interventions —
ER/LA Opioid Analgesic REMS

July 9, 2012
Approval of
ER/LA Opioid
REMS

• Central component
  – Education component for prescribers
  – Required content in a “Blueprint” created by FDA

• Metrics to be used to determine success include:
  – Numbers of providers who successfully complete the CE
  – Changes in patterns of opioid use/abuse
  – Knowledge surveys

• Advisory committee – May 2016 discussed impact
Reach of the REMS Intervention

- Large absolute number trained
- Small proportion of ER/LA prescribers had completed training
- Direct linkages to prescribing practices were not available
- What population-based impact could we expect based on these findings?
Summary of Assessment Findings

Prescription volume declining
• Does not address appropriateness of prescribing

Decreases In Outcomes Began Before REMS Implemented

Example 1: ER/LA opioid related poison center exposure calls
Example 2: Recent ER/LA opioid abuse in people entering opioid addiction treatment

Decreases in adverse outcomes
• Began before REMS was implemented

Source: https://www.fda.gov/media/97531/download
Complicated path from intervention to measured outcomes

- Even desirable changes in prescriber and patient behavior may have mixed effects on population outcome measures.

<table>
<thead>
<tr>
<th>Desired effects on prescriber/patient behavior</th>
<th>Possible effects on surveillance measures</th>
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</thead>
<tbody>
<tr>
<td>Safer opioid storage and disposal—Fewer available for abuse</td>
<td>↓ treatment center abuse rates</td>
</tr>
<tr>
<td>Improved recognition of abuse/addiction—more referrals to treatment</td>
<td>↑ treatment center abuse rates</td>
</tr>
<tr>
<td>Safer opioid dosing and use</td>
<td>↓ ED visit and poison center call rates?</td>
</tr>
<tr>
<td>Earlier recognition of overdose symptoms</td>
<td>↑ ED visits and poison center call rates?</td>
</tr>
</tbody>
</table>
REMS Assessment to Date: Scope of the REMS Education

• FDA determined that two things were needed to modify the REMS and informed industry:
  – Expand the REMS to include IR opioid analgesics
    • Approved September 2018
  – Expand the education to include additional healthcare workers and to provide info about pain management and non-pharmacologic treatment of pain
    • FDA modified the REMS ‘Blueprint’ to guide the educational content
Challenges

• Better data!
  – Difficult area to study because behaviors are covert and often hidden from the health care system
  – Have pockets of data – not nationally representative
  – Better insights into behaviors all along continuum of behaviors

• Data linked to connect exposures with outcomes
  – Often collected in different systems (pharmacies vs medical examiners vs hospitals)
  – HHS working on this with national level data; FDA funding work in state of CT

• Improved methods
  – What is appropriate denominator for measuring and comparing abuse rates?
Questions?
Thank you