Challenges and Data Needs in Assessing the Impact of Packaging, Storage, and Disposal Options after an Opioid Drug Product is Marketed

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Overview

• Framing
• Questions
• Relevant Populations
• Epidemiologic Study Designs
• Some Postmarketing Data Sources
• Capturing Exposures and Outcomes
• Main Messages
Framing: Evaluating Formulations with Abuse Deterrent Properties

Public Meeting, July 10-11, 2017:

Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting

https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm
QUESTIONS ABOUT THE USE AND IMPACT OF PACKAGING, STORAGE, AND DISPOSAL SOLUTIONS IN THE POSTMARKET SETTING

Accidental Exposure

Misuse

Third Party Access

Excess Supply

DESCRIPTIVE QUESTIONS

WHO?
WHAT?
WHERE?
WHEN?
WHY?
HOW?
Effective in the Real World?

Compared to What??

- Accidental Exposure
- Misuse
- Third Party Access
- Excess Supply

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752
Relevant Populations

Accidental Exposure

Non-Patients:
- Young children

Patients:
- Elderly
- Cognitive impairment
- Adolescents
- Naïve to opioids
- High risk of SUD
- Existing SUD

Misuse

Third Party Access

Non-Patients:
- Household members
- Adolescents
- Friends
- Visitors
- Healthcare workers
- "Black market"

Excess Supply

SUD = substance use disorder
Epidemiologic Study Designs

Study types

Descriptive
- Goal
  - Hypothesis generating
  - Burden of disease
  - Population level
    - Ecologic
  - Individual level
    - Qualitative/ethnographic
    - Case reports/series
    - Cross sectional surveys

Analytical
- Goal
  - Hypothesis testing
  - Etiology of disease
  - Evaluate interventions
  - Observation

Experimental
- Randomized controlled trials
  - Prospective

Cohort studies
- Prospective
- Retrospective

Case-control studies
- Prospective
- Retrospective

Self-controlled studies
- Case-crossover
- Self-controlled case series
<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO</strong> uses the packaging, storage, disposal options?</td>
<td>Qualitative, Quantitative, Ethnographic</td>
</tr>
<tr>
<td><strong>WHAT</strong> options are being used?</td>
<td></td>
</tr>
<tr>
<td><strong>WHERE</strong> are they being used?</td>
<td></td>
</tr>
<tr>
<td><strong>WHEN</strong> are they being used?</td>
<td></td>
</tr>
<tr>
<td><strong>WHY</strong> are they being prescribed/added?</td>
<td></td>
</tr>
<tr>
<td><strong>HOW</strong> are they being used?</td>
<td></td>
</tr>
<tr>
<td>Barriers to use and unintended consequences</td>
<td></td>
</tr>
</tbody>
</table>
Ecologic Studies

2008-2010

2011-2015

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752
Individual-Level Analytic Studies

CASE-CONTROL

TIME

COHORT

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752

Misuse
Accidental Exposure
Excess Supply
Third Party Access
Pragmatic Trials

Randomize Exposure to Option

Patient-level?

Household-level?

Misuse

Accidental Exposure

Excess Supply

Third Party Access

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752
Some Types of Data Used in the Postmarket Setting

- Electronic Health Data
- Other Utilization Data
- Surveys/Interviews
- Other Data Sources
Electronic Health Data

- Electronic health records
- Medical/prescription administrative claims
- Inpatient health records
Electronic Health Records

• **Type of prescription/packaging information**
  – Product name
  – Specific package order (?) or free-text notes on specific packaging directions for patient

**Reason for prescription/packaging**
  – Diagnosis/procedure codes
  – Free-text notes

• **Outcomes**
  – Diagnosis/procedure codes
  – Vitals and lab results
  – Free-text notes

• **Caveats**
  – Possibly a single provider or group of providers; missing whole picture
  – Diagnosis/procedure codes for billing purposes
  – Free-text notes are hard to analyze
  – Actual product dispensed unknown
Administrative Claims

• **Type of prescription/packaging information**
  – NDC code identifies drug & manufacturer packaging

• **Reason for prescription/packaging**
  – Diagnosis/procedure codes

• **Outcomes**
  – Diagnosis/procedure codes

• **Caveats**
  – Diagnosis/procedure codes for billing purposes
  – Actual product dispensed known, but don’t know what was prescribed or how opioids ultimately used
  – Unclear whether will be “NDC” just for package added by pharmacist

# National Drug Code (NDC)

**10-digits, 3-segments**  
*Transformed to 11-digits (5-4-2, no dashes)*

<table>
<thead>
<tr>
<th>Labeler Code (4-5 digits)</th>
<th>Product Code (3-4 digits)</th>
<th>Package Code (1-2 digits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallinckrodt, Inc.</td>
<td>5mg/325mg oxycodone HCl/acetaminophen tablets</td>
<td>500 tablets</td>
</tr>
<tr>
<td>0406</td>
<td>0512</td>
<td>05</td>
</tr>
</tbody>
</table>

Manufacturing, repackaging, or distributing firm  
Active moieties, strength, dosage form, & formulation  
Package form & size
Inpatient Health Records

- Records what happened during the hospitalization
- Information available varies according to the EHR system used and the hospital
- Type of prescription/packaging information
  - NDC code identifies drug & manufacturer packaging
  - Other supply chain systems or automated dispensing cabinet data?
- Outcomes
  - Diagnosis/procedure codes
  - Vitals and lab results
  - Free-text notes within the EHR during hospitalization
- Caveats
  - Each hospital may have unique EHR or supply chain/automated dispensing data
  - Diagnosis/procedure codes are for billing purposes
  - Free-text difficult to analyze
  - Prior exposures, outcomes, and health conditions may not be in the hospital records
Other Utilization Data

• Pharmacy transaction records
  – Retail pharmacy dispensing
  – Prescription Drug Monitoring Programs (PDMP)

• Sales data
  – Distribution to retail pharmacies (back-door of the pharmacy)
  – End-user retail sales
    • Out the front door of the store (point of sale data)?
    • On-line sales?
Surveys/Interviews

- Big national surveys (e.g., National Survey on Drug Use and Health, Monitoring the Future, Youth Risk Behavior Surveillance System)
- Enriched populations (e.g., treatment center surveys, online drug discussion forums)
- Internet panel surveys using market research survey panels
- Provider, pharmacist, patient surveys
## Selected National Health Surveys

Add questions about “options” to existing national health surveys?

<table>
<thead>
<tr>
<th>Survey</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Survey on Drug Use and Health (NSDUH)</td>
<td>Household survey ≥ age 12 years</td>
</tr>
<tr>
<td></td>
<td>Misuse of prescription opioids + reason</td>
</tr>
<tr>
<td></td>
<td>Limited product-specific data</td>
</tr>
<tr>
<td>Monitoring the Future</td>
<td>School-based survey on adolescent drug abuse</td>
</tr>
<tr>
<td></td>
<td>Limited product-specific data</td>
</tr>
<tr>
<td></td>
<td>Longitudinal follow-up component</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey</td>
<td>Interviews, physical exam, labs</td>
</tr>
<tr>
<td></td>
<td>Longitudinal follow-up component</td>
</tr>
<tr>
<td></td>
<td>Prescription drug use and whether interviewer saw medication container</td>
</tr>
<tr>
<td>Behavioral Risk Factor Surveillance System</td>
<td>Telephone survey of &gt;400,000 adults per year</td>
</tr>
<tr>
<td></td>
<td>Core, optional, and state-added questions</td>
</tr>
<tr>
<td></td>
<td>Use of narcotics other than heroin</td>
</tr>
<tr>
<td>Youth Risk Behavior Surveillance System</td>
<td>School-based survey -- health risk behaviors</td>
</tr>
<tr>
<td></td>
<td>National, state and district level data</td>
</tr>
<tr>
<td></td>
<td>Pain medication use without prescription/differently than prescribed</td>
</tr>
</tbody>
</table>
Enriched Populations: Treatment Center Surveys

- Includes those entering or being assessed for substance use disorder treatment
  - Captures a hard-to-reach population of high-risk individuals
  - Can provide product-specific patterns of abuse

- Caveats
  - Drug may be separated from packaging or storage options
  - Packaging/storage not currently captured
  - Difficult to define underlying population
  - Generalizability of results is unclear
Internet Panel Surveys

• Survey administration company invites individuals to subscribe to online survey panel
• Members opt-in for specific surveys
• Existing surveys ask about intentional misuse and abuse
• Flexible surveys, can more easily add questions about packaging, storage, and disposal options
• Caveats
  – Generalizability of results is unclear (who participates?)
  – People may misremember or intentionally report incorrect responses
Provider, Pharmacist, Patient Surveys

- May be the only way to capture some options and outcomes (e.g., intentional misuse)

Caveats:
  - Usually small and generalizability may be poor
  - People may misremember or intentionally report incorrect responses
Other Data Sources

• Poison Control Centers
  – Product-specific information but does not currently capture separate packaging/storage information
  – Generalizability is unclear (who calls?)
  – Severe overdoses and immediate deaths unlikely to generate a call

• Mortality Data
  – Packaging, storage, and disposal options unlikely to be recorded

• Emerging Technologies?
  – Packaging that captures when the package is accessed or medication is consumed could help establish patterns of misuse
Capturing Exposures
(Opportunity for contact with the “option” by the patient or a third-party)
Third Party Access - Inpatient
Excess Supply Feeds Other Problems

- Accidental Exposure
- Misuse
- Third Party Access
- Excess Supply

- Lack of Secure Storage
- Lack of Disposal
Capturing Outcomes
One Possible Hypothetical Sequence of Events For...

Accidental Exposure
- Child Finds Package
- Opens Package
- Consumes Tablet
- Overdoses
- ED/Hospital
- Death

Unintentional Misuse
- Patient Forgets Dose
- Multiple Doses
- Overdoses
- ED/Hospital
- Death

Intentional Misuse
- Uses for Other Pain
- Develops Tolerance
- Self-Increases Dose
- Develops Addiction
- Multiple Doctors
- Overdoses
- ED/Hospital
- Death

Third Party Access – Teenager
- Teen Finds Medication
- Opens Package
- Uses to Get High
- Addiction
- Overdoses
- ED/Hospital
- Death

Third Party Access – Healthcare Worker
- Nurse Accesses Vial
- Replaces Contents
- Administers to Patient
- Patient Gets Infection

ED = emergency department; EHR = electronic health record
Main Messages

• Designing studies to assess utilization and real-world effectiveness of the options may be challenging
  – Existing data systems may not capture exposure to the option, especially in the relevant population
  – Data sources may not exist to link exposure and outcome in the same person
  – Some of the problems that we’re targeting are very difficult to measure (e.g., intentional misuse)
  – We may need more proximal outcomes or surrogates for outcomes to efficiently study these problems
  – May need to generate new data for proximal outcomes