Evaluating the Impact of Abuse Deterrent Formulations: Methodological Challenges in Postmarketing Data

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The opinions in this presentation are my own and do not necessarily reflect the views and policies of the FDA
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  – Much of the technical work on the postmarketing studies presented in these slides is hers, but she was unable to be here to present today
Outline

• Background/regulatory framework
• Current challenges in postmarketing studies
  – Data sources
  – Methods and analytic approaches
• Case studies
• Path forward
Background and Regulatory Framework
Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics*
Products from U.S. Outpatient Retail Pharmacies


* Includes all schedule-II opioid analgesics based on scheduling status in 2016.
**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

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FDA Opioids Action Plan

• Expand the use of advisory committees
• Develop warnings and safety information for immediate-release (IR) opioid labeling
• Strengthen postmarket requirements to get needed data
• Update Risk Evaluation and Mitigation Strategy (REMS) Program for Prescription Opioids
• Expand access to abuse-deterrent formulations (ADFs) to discourage abuse
• Support better treatment for prescription opioid abuse and overdose
• Reassess the risk-benefit approval framework for opioid use

--www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm
Products with approved abuse-deterrent labeling

• Based on *in vitro* and *in vivo* premarket data, ten opioid products labeled as having properties *expected to deter abuse*:

<table>
<thead>
<tr>
<th>OxyContin</th>
<th>Xtampza ER</th>
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<tbody>
<tr>
<td>Targiniq ER</td>
<td>Troxyca ER</td>
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<tr>
<td>Embeda</td>
<td>Arymo ER</td>
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<tr>
<td>Hysingla ER</td>
<td>Vantrela ER</td>
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<tr>
<td>MorphaBond</td>
<td>Roxybond (<em>first IR</em>)</td>
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• All have postmarket requirements (PMRs) to evaluate the impact of these properties on abuse in the “real-world” post-approval setting
Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesic Products* with abuse deterrent properties from U.S. Outpatient Retail Pharmacies


*Not marketed during study period: Targiniq (oxycodone/naloxone ER) - Approved 07/2014; MorphaBond (morphine ER) - Approved 10/2015; Troxyca (oxycodone/naltrexone ER) - Approved 08/2016 – Roxybond (oxycodone IR) – Approved 04/2017

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Goal of Postmarket Evaluation of Opioids with Abuse-deterrent Properties
(from FDA Guidance for Industry)

“Goal of postmarket studies is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting...Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.”

Postmarket Evaluation of Opioids with Abuse-deterrent Properties
(from FDA Guidance for Industry)

• **Formal studies**
  – Hypothesis-driven
  – Meaningful measures of abuse *(including route)* and related adverse outcomes
  – National or multiple large geographic regions
  – Sufficiently powered to examine trends

• **Supportive information**
  – Can be qualitative, descriptive, smaller
  – Provide context, aid interpretation of formal studies
Postmarket Evaluation of Opioids with Abuse-deterrent Properties

• Recently moved to 2-phase approach:

**Phase 1:**
Descriptive
Provide surveillance data on utilization, scope, and patterns of abuse

**Phase 2:**
Hypothesis Testing
Once market uptake is sufficient, conduct studies to evaluate for meaningful reduction in abuse and related outcomes
Postmarket Abuse-deterrent Labeling

• Labeling dictates how a product can be legally marketed

• Claims in drug labels require
  – High quality studies (but here we don’t have RCTs!)
  – In-depth FDA review
  – Often, public discussion and outside expert input

• Goal is to provide clinicians and policymakers full and balanced information

• Currently, no opioid product label states that it reduces abuse in the community (Category 4 labeling) – only that it is “expected” to do so, based on pre-market evaluations
Challenges
How is abuse different from traditional pharmacoepidemiology safety outcomes?

• Abuse and related outcomes occur in patients and non-patients
• Traditional data sources (claims/EMR) are specific to patients under medical care
• Abuse is covert behavior—not captured well in these sources
• Outcomes associated with drug abuse are social/legal, as well as medical—manifest in multiple settings
Pathways to Abuse/Misuse of Prescription Drugs and Related Adverse Outcomes

Drug manufactured → Drug distributed → Drug prescribed/dispensed

Drug diversion

Inappropriate use by patients

Patient supply

Patient use as prescribed

Abuse
Misuse
Addiction
Overdose
Death

Outcome captured in...

Population Surveys (self-report)
Health Care Utilization data
Mortality Records

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)
Challenges with Current Postmarketing Data used to Evaluate Abuse-Deterrence

- Most studies use ecologic time series design: pre-post comparison of abuse rates
- Goal is to isolate effect of abuse-deterrent formulation, support causal inference
- Must minimize other changes over time that could bias/confound pre-post comparison
  - Changes in study population (sampling/selection bias)
  - Changes in ascertainment (misclassification/information bias)
- Secular trends in
  - Prescribing patterns/utilization
  - Opioid abuse landscape (Rx. Opioids, heroin, fentanyl)
  - National/state/local interventions
Challenges with Current Postmarketing Data used to Evaluate Abuse-Deterrence

• No nationally-representative data that can reliably estimate national abuse, addiction, overdose rates for specific opioid products – by route
• Attempt “mosaic approach,” looking for consistency in multiple imperfect data sources
• Currently available data sources have significant limitations that can bias pre-post comparisons over time
• Focus today on two sources we see most often
  • Poison Control Center call data
  • Surveys of individuals entering or being assessed for treatment
Poison Control Center Data

**Key Strengths**
- National or near-national coverage
- Meaningful outcomes: abuse/misuse associated with some adverse effect

**Key Challenges**
- Unclear what factors influence whether call is made
- Capture small, unknown fraction of abuse/overdose
  - Vary over time for given product?
  - Vary across products?
- Poor ascertainment of generic products –may be reported as well-recognized brand name
- No capture out-of-hospital, unattended overdose deaths (likely most opioid deaths)
Surveys of people entering or being assessed for substance use disorder treatment

<table>
<thead>
<tr>
<th>Key strengths</th>
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<tr>
<td>Enriched population—can get detailed info on route of abuse</td>
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<tr>
<td>Flexible/adaptable to changing market</td>
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<tr>
<td>Captures detailed info on abuse of specific products</td>
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<table>
<thead>
<tr>
<th>Key Challenges</th>
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<tbody>
<tr>
<td>Non-representative convenience samples--subject to bias</td>
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<td>Geographic distribution changes over time</td>
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<td>Population mix changes over time due to changes in distribution of types of participating sites (e.g., public/private, inpatient/outpatient)</td>
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<td>Patterns seen may not reflect abusers more broadly</td>
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<td>Frequent changes in survey -- question wording, order, etc.</td>
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<tr>
<td>Can bias trends, pre-post comparisons</td>
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<tr>
<td>Misclassification—may be substantial and differential</td>
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<tr>
<td>IR/ER, original/reformulated, generic/brand, opioids with similar name or pill appearance</td>
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Challenges in Analytic Approaches:
What is best metric?

- **Route of abuse (ROA) profile** = Proportion of people abusing a drug who report abusing it via specific routes

- **Population rate/prevalence** = abuse calls/mentions as a proportion of study population (e.g., per 100,000 residents, per 100 assessments)

- **Prescription or tablet-adjusted abuse rate** = abuse mentions for a drug per 10,000 prescriptions/tablets dispensed

Factors that might influence prescribing patterns and trends:

- **Product reformulation**
- Drug shortages
- Availability of generics
- Advertising
- Use of PDMPs

- Insurance coverage, preferred status
- Law enforcement actions (e.g., “pill mill” crackdowns)
Challenges in Analysis and Interpretation: What is best metric?

• Adjusting for changes in drug utilization
  – controls for secular trends in prescribing unrelated to product reformulation—if don’t adjust, pre-post analyses may be confounded, BUT
  – also controls for changes caused by product reformulation (reduced demand by those intending to abuse/divert)—pre-post analyses may be biased toward null

• Is the “truth” somewhere in between? Is a range of estimates the best we can expect when evaluating the impact of drug reformulation?
Challenges in Analysis and Interpretation: Accounting for Secular Trends

- Means analysis with comparator

![Mean Abuse Rate Chart]

- Pre-period
- Post-period

Drug
Comparator

Effect of reformulation?
Challenges in Analysis and Interpretation: Accounting for Secular Trends

The problem with means analyses...

Can see big change in mean abuse rates, even with no effect—all secular trend
Challenges in Analysis and Interpretation: Accounting for Secular Trends

The problem with means analyses...

Or no change in mean, even if big effect
Challenges in Analysis and Interpretation: Accounting for secular trends

• Interrupted time-series analyses (ITS)

![Graph showing changes in levels and slopes over time.]

- Drug reformulated
- Change in level: Immediate effect
- Change in slope: “Bending the Curve”
Challenges in Analysis and Interpretation: Accounting for secular trends

• Adding comparator(s)

• Interpreting results gets pretty complicated—Meaningful reduction in abuse??
Challenges in Analysis and Interpretation: Accounting for secular trends

• Typically no ideal comparator
  – Different baseline abuse levels/trends
  – Major market changes during study period
  – Problems with ascertainment
    • E.g., difficulty distinguishing single-ingredient from combination IR oxycodone in data sources

• Multiple comparators?
  – Complicates interpretation, causal inference

• Composite comparator?
  – Composition can change over time
Case Studies
Case Study: Opana ER

• Postmarketing data suggest 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 anecdotal information from outbreak investigations
Case Study: Opana ER

• This shift occurred on backdrop of sharp increases in Opana ER abuse rates during pre-period
  – Some data suggest overall abuse rates declined after reformulation
  – Unclear whether, overall, Opana ER injection abuse rates increased more than they would have without the reformulation
  – Some data suggested equally high injection abuse rates and higher nasal abuse rates for generic ER oxymorphone (without abuse-deterrent properties)
  – Increases driven by certain geographic regions (esp. Tennessee/Appalachia)
Case Study: Opana ER

- IV abuse of reformulated Opana ER associated with serious blood disorder resembling thrombotic thrombocytopenic purpura (TTP)
- Properties of the drug and tampering practices may have increased risk of HIV/hepatitis C transmission and contributed to unprecedented HIV outbreak in rural Indiana
- Advisory committee voted 18:8 that benefits of reformulated Opana ER do not outweigh risks
- FDA currently having internal discussions about best course of regulatory action, given complexity of postmarketing evidence
Case Study: OxyContin

• Was first opioid with abuse-deterrent properties in labeling
• Most widely used of products with such labeling
• Much published literature, most of it positive although most also supported and/or authored by Purdue
• FDA-required PMR studies ongoing
• FDA epidemiology and biostatistics reviewers working with Purdue to refine study protocols, try to address many challenges
• Possible public discussion of these study results in 2018
Path Forward
Path Forward

- FDA continues to support development of effective abuse-deterrent opioid products and rigorous evaluation of their impact -- just one part of multi-pronged effort to address opioid crisis
  - Continue to work with drug manufacturers through PMRs to improve postmarket studies – publicly share results
  - Working with other federal agencies to develop new data resources and enhance existing ones
    - NCHS/SAMHSA – National Hospital Care Survey
    - CDC - NEISS/CADES
    - NCHS - Extraction of specific drugs from literal text on death certificates
Path Forward

– FDA contracted access to poison control center and treatment center data in 2016
  – AAPCC, RADARS treatment centers, NAVIPPRO
– Broad Agency Announcement (BAA) issued in 2016, soliciting research proposals in this area
– Public scientific meeting this summer
  – How best to address current challenges in this area
  – Development of better data sources, linkages, study designs, outcome measures