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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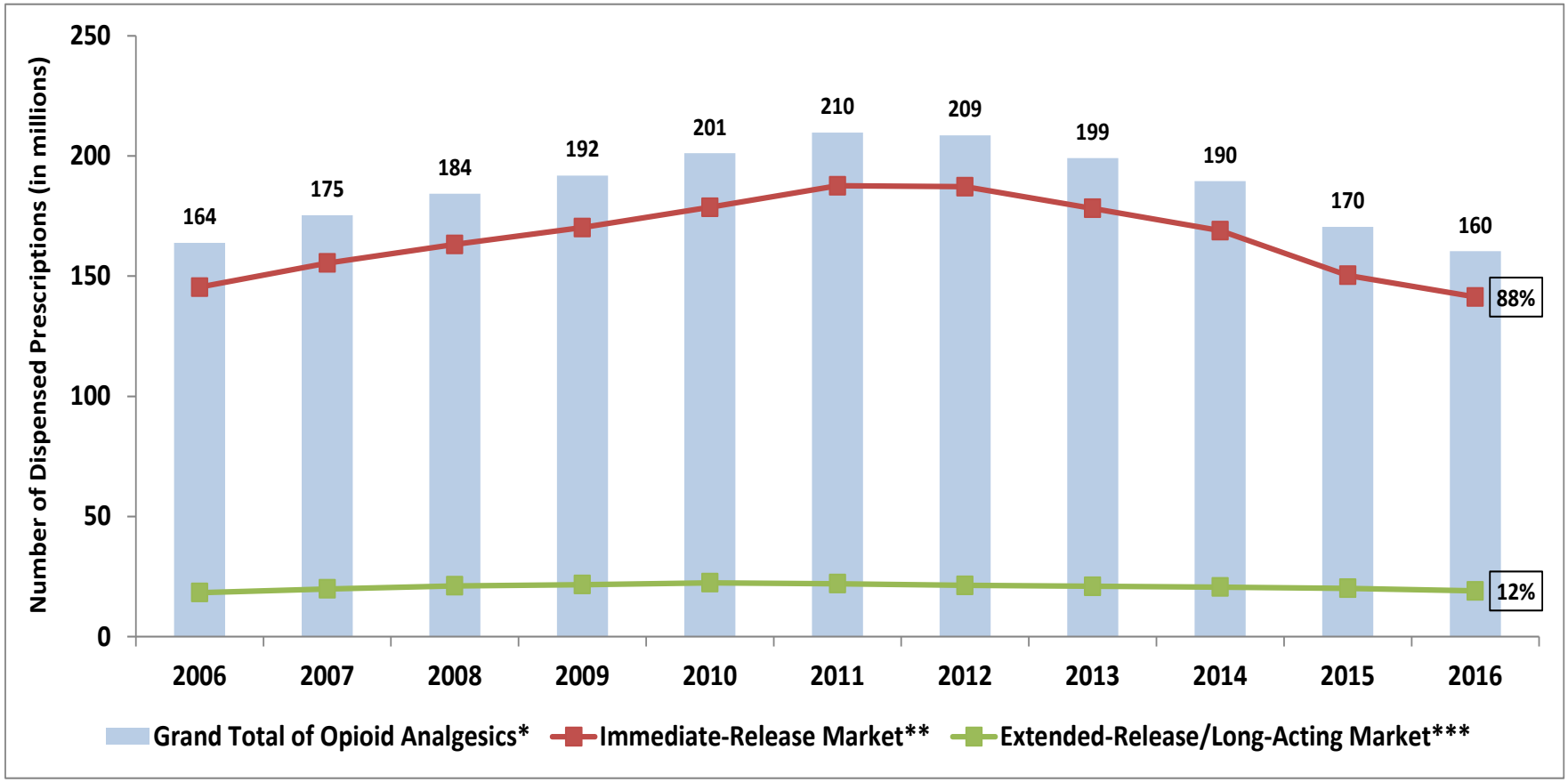
  - Much of the technical work on the postmarketing studies presented in these slides is hers, but she was unable to be here to present today

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



Source: National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2016 Extracted March 2017.
* 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

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

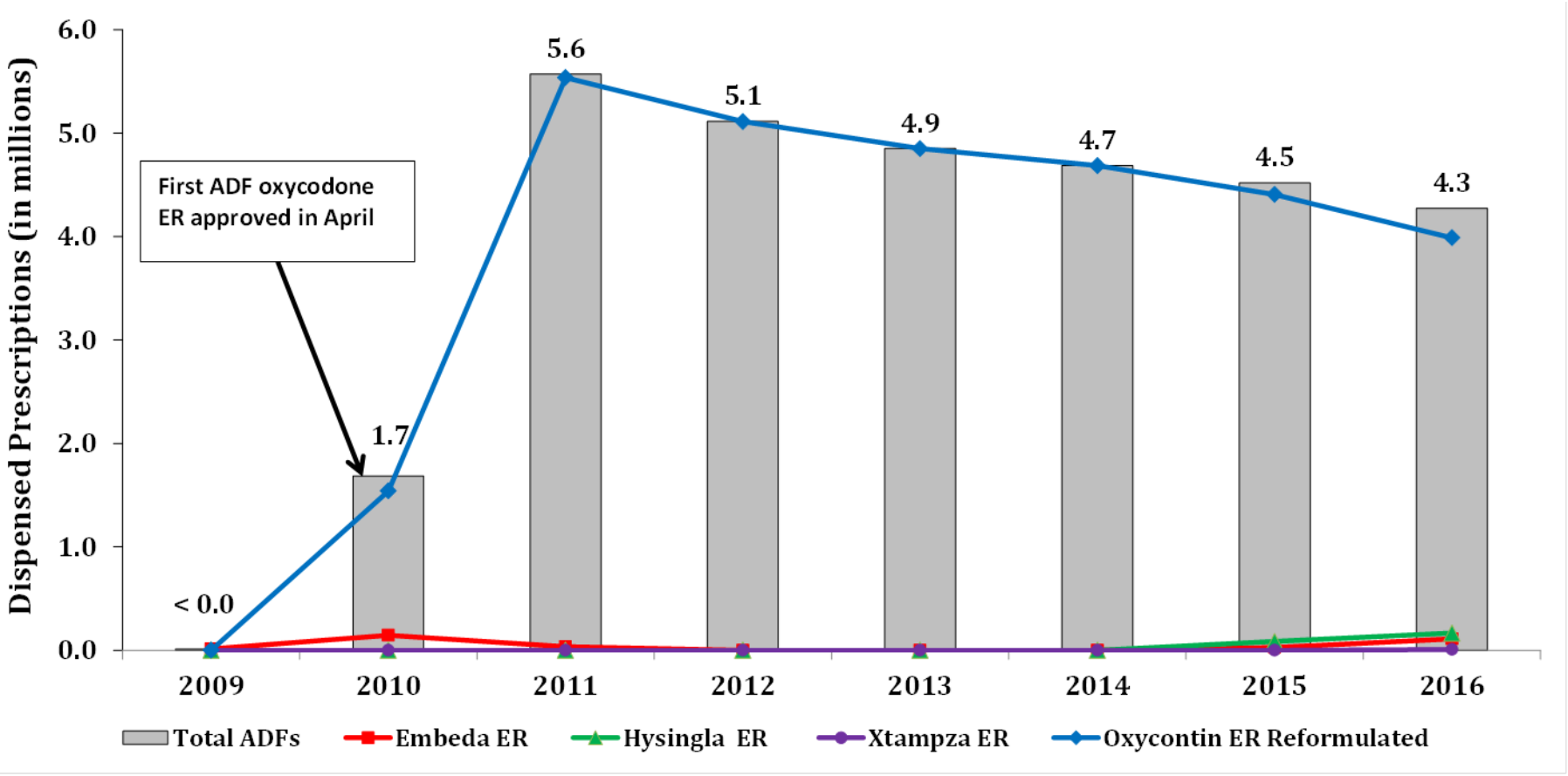
Products with approved abuse-deterrent labeling

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

OxyContin	Xtampza ER
Targiniq ER	Troxyca ER
Embeda	Arymo ER
Hysingla ER	Vantrela ER
MorphaBond	Roxybond *(first IR)*

- 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



Source: QuintilesIMS National Prescription Audit™, Years 2009-2016. Data Extracted March 2017.

*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

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 consider a meaningful reduction."

1. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry," FDA Center for Drug Evaluation and Research, April 2015

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

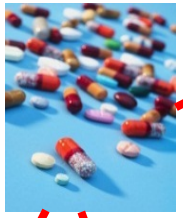
Challenges

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



Patient supply

Drug manufactured

Drug distributed

Drug prescribed/ dispensed

Patient use as prescribed

Drug diversion

Inappropriate use by patients

Abuse

Misuse

Addiction

Overdose

Death

Outcome captured in…

Population Surveys (self-report)

- Nationally-representative household and school surveys
- Treatment center surveys
- Internet surveys

Health Care Utilization data

- Poison Center data
- Emergency Department Visit and Hospitalization data (claims, EMR)
- Addiction treatment admissions

Mortality Records

- 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

- Key strengths
  - Enriched population—can get detailed info on route of abuse
  - Flexible/adaptable to changing market
  - Captures detailed info on abuse of specific products

- Key Challenges
  - Non-representative convenience samples--subject to bias
    - Geographic distribution changes over time
    - Population mix changes over time due to changes in distribution of types of participating sites (e.g., public/private, inpatient/outpatient)
    - Patterns seen may not reflect abusers more broadly
  - Frequent changes in survey -- question wording, order, etc.
    - Can bias trends, pre-post comparisons
  - Misclassification—may be substantial and differential
    - IR/ER, original/reformulated, generic/brand, opioids with similar name or pill appearance

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:

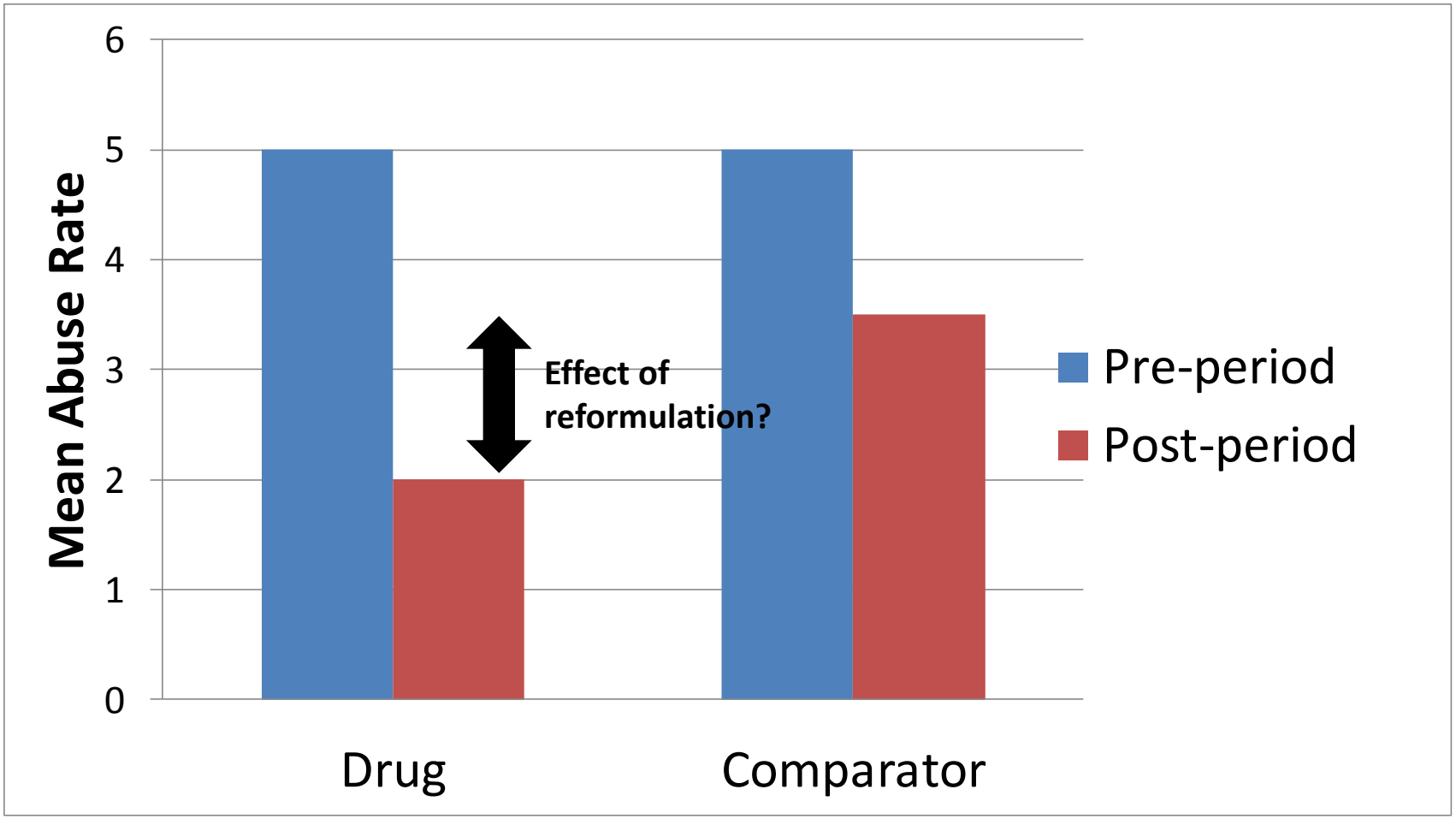
- **Product reformulation**
- Drug shortages
- Availability of generics
- Advertising
- Use of PDMPs
- Insurance coverage, preferred status
- Law enforcement actions (e.g., "pill mill" crackdowns)

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?

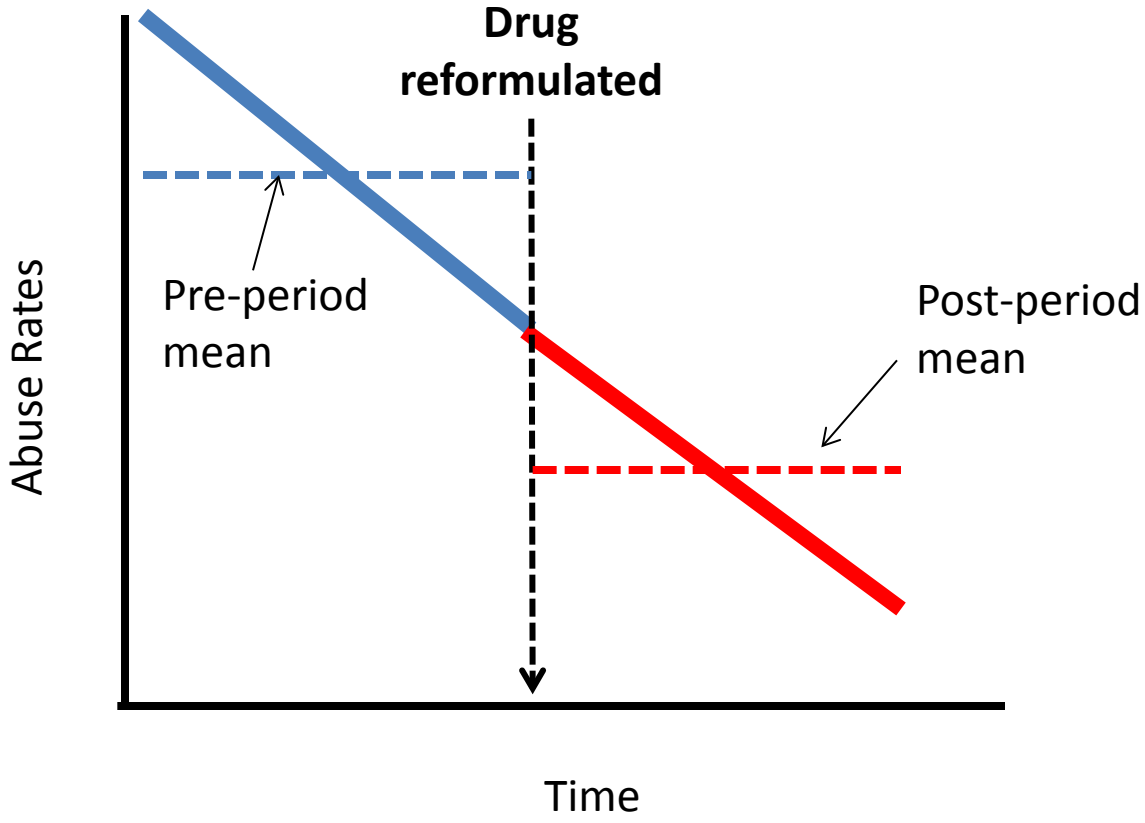
Challenges in Analysis and Interpretation: Accounting for Secular Trends

- Means analysis with comparator



Challenges in Analysis and Interpretation: Accounting for Secular Trends

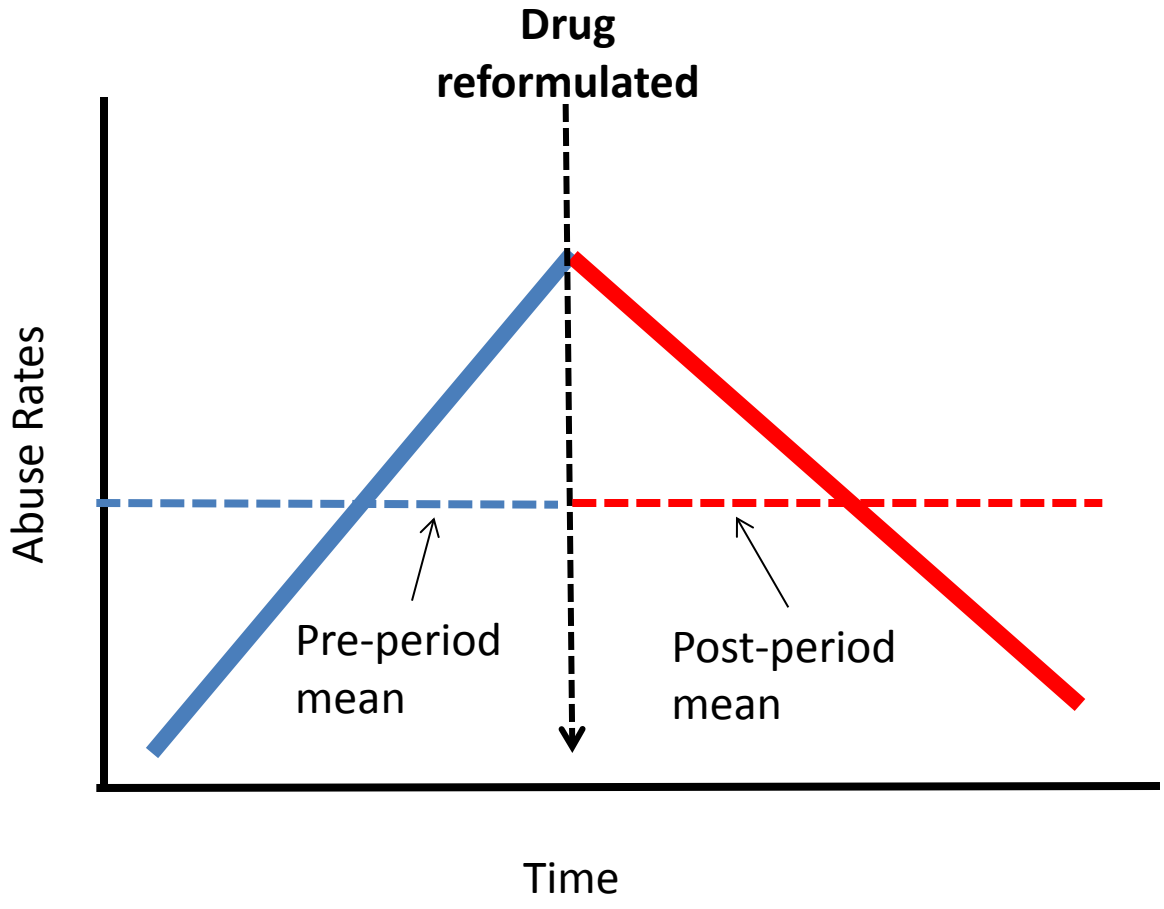
The problem with means analyses…



Can see big change in mean abuse rates, even with no effect—all secular trend

Challenges in Analysis and Interpretation: Accounting for Secular Trends

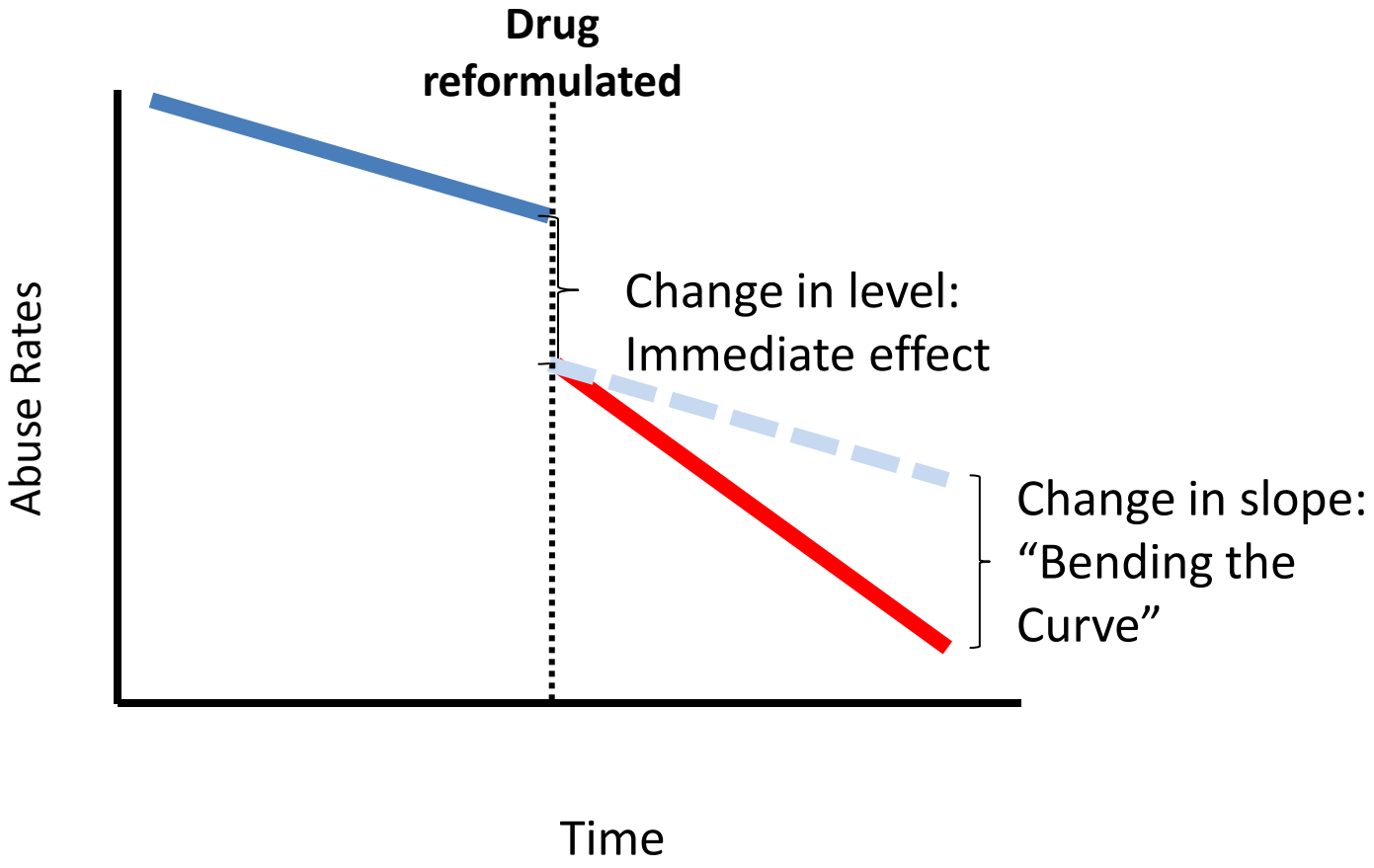
The problem with means analyses…



Or no change in mean, even if big effect

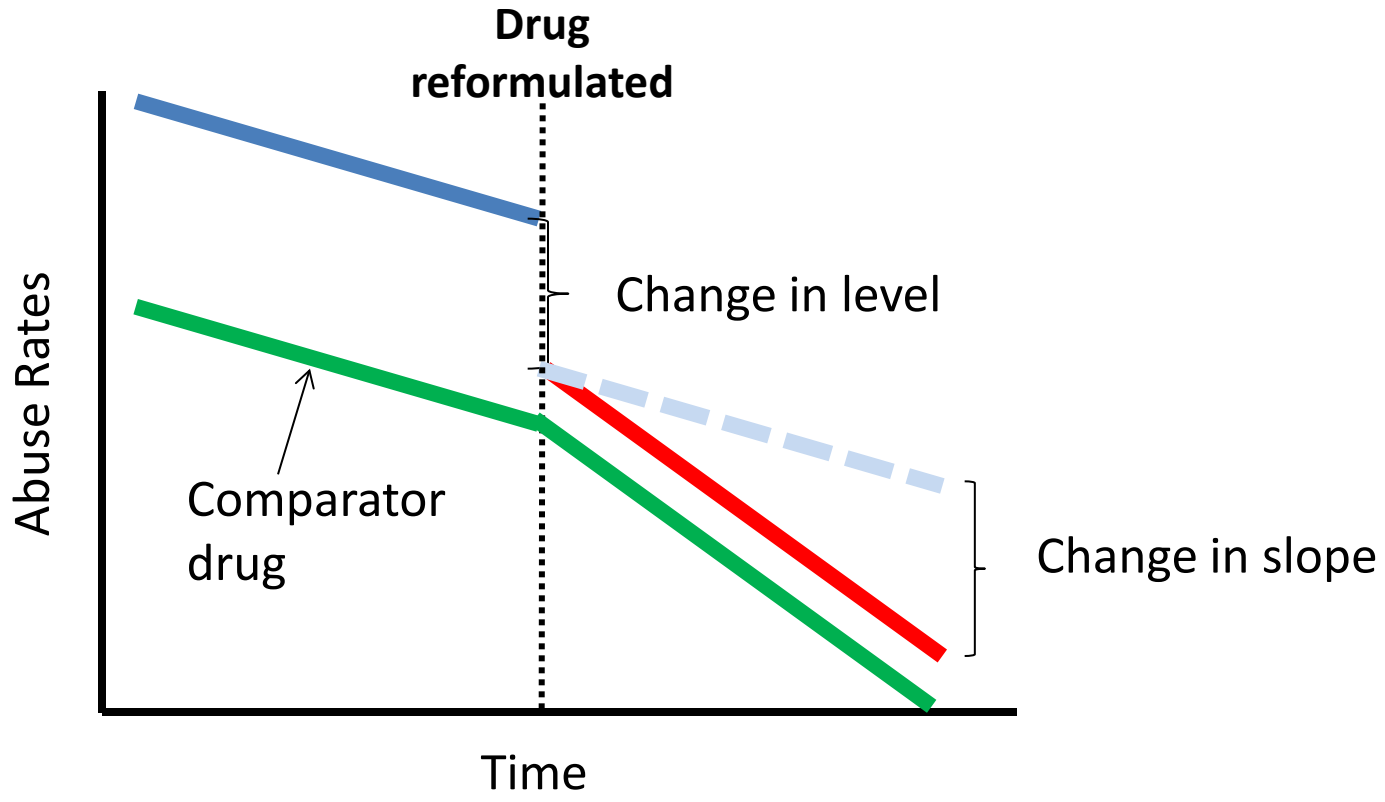
Challenges in Analysis and Interpretation: Accounting for secular trends

- Interrupted time-series analyses (ITS)



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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