Pharmacoepidemiologic Research on Drugs of Abuse

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The Opioid Crisis and Pharmacoepidemiology

• A societal problem
• Misuse, opioid use disorder, abuse, overdose and death are drug safety issues
• Involves both patients to whom an opioid was prescribed and others in household/community
• Difficult to study and quantify

Source: https://www.hhs.gov/opioids/about-the-epidemic/index.html
Basic Pharmacoepidemiologic Concepts and Opioids

**Exposure**
- Variable dosing
- Intermittent dosing
- Formulations vs active moiety
- Units vs prescriptions vs MMEs

**Outcome**
- Many outcomes of interest
- Outcomes are distinct but related to each other
- Not all are medically attended
- Not all are documented in medical records

**Confounders**
- Indication for use not systematically recorded
- Multiple medications and other substances
- Varying local and regional policies
- Rapidly changing landscape

**Populations**
- Geographic variations
- National data are not granular
- Granular data are in narrow populations
- Use by patients and household/community
What is the question?

Data sources and approaches depend on the question

1. **Signal detection and assessment**
   - Do we see emerging reports of abuse with drug X?
   - Are there new/unrecognized AEs associated with drug X under the context of abuse?

2. **Descriptive population data on abuse and related outcomes**
   - Scope (public health burden)
   - Trends (getting better or worse)
   - Patterns (routes of abuse, demographic/geographic distributions)
   - Characterize AEs associated with abuse

3. **Comparative analysis, hypothesis testing**
   - Is drug X more likely to be abused than drug Y?
   - What is the impact of a particular intervention?
Exposure
(signal, descriptive, comparative)
Population Measures of Exposure

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<th>Number of MMEs</th>
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<td>1</td>
<td>10</td>
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<td>1</td>
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<td>75</td>
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<tr>
<td>1</td>
<td>5</td>
<td>400</td>
<td>600</td>
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</table>

Morphine sulfate extended release – 10 mg
Morphine sulfate extended release – 200 mg
Oxycodone hydrochloride – 5 mg
Oxycodone hydrochloride extended release – 80 mg
## Opioid Exposure Measures are Multidimensional

### Table 1. Nationally Estimated Annual Number of Opioid Analgesics Dispensed in Number of Morphine Milligram Equivalents (MME in B), Total Prescriptions (Rx in M), and Prescriptions Dispensed Adjusted for the U.S. Census Population, by Brand (Brand and Branded Generics) and Generic Products from U.S. Outpatient Retail Pharmacies

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<td>Total Rx</td>
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<td>Brand Rx</td>
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<td>232 M</td>
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<td>Rx per 100 population</td>
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<td>56</td>
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<td>63</td>
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<td>69</td>
<td>72</td>
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<td>MME per Rx</td>
<td>70 B</td>
<td>79 B</td>
<td>87 B</td>
<td>105 B</td>
<td>121 B</td>
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<td>227 B</td>
<td>244 B</td>
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<td>234 B</td>
<td>224 B</td>
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<tr>
<td>MME per capita</td>
<td>256</td>
<td>284</td>
<td>311</td>
<td>373</td>
<td>424</td>
<td>467</td>
<td>520</td>
<td>572</td>
<td>618</td>
<td>608</td>
<td>662</td>
<td>707</td>
<td>740</td>
<td>791</td>
<td>771</td>
<td>745</td>
<td>708</td>
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</table>

Estimates were derived from total U.S. Census population projections and estimates and IQVIA, National Prescription Audit. Prescriptions dispensed per 100 persons adjusted to the U.S. Census population. Brand: all trade name products including brand and branded generic products. Excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products. B = billions; M = millions.

### Source
A Word on Morphine Milligram Equivalents

• Originally intended to assist clinicians in determining initial dose when converting a patient’s opioid therapy
  – Broad indicator of relative analgesic potency
  – Based on small studies
• Relevance to abuse potential not fully worked out
• Large variability amongst prescribers
  – Survey of 319 HCP (25% MD, 57% PharmD, 16% NP/PA) converted 5 opioid analgesic doses to morphine equivalents using reference of choice
  – Significant variation in opioid conversions for some opioids

Challenges in Using Healthcare Claims Data to Study Opioid Exposures

• Exposure ascertainment incomplete
  – Accurate record of drug substance/product dispensed to the patient
  – Other patient opioid exposures not captured
  – Dosing estimation inaccurate
    • PRN dosing
    • Development of tolerance over time, or OUD
  – No exposure ascertainment for other individuals with access to the prescribed opioids
  – Changes in coverage policies over time
    • Days’ supply variable in claims affected by policies – may no longer be accurate
Formulations and Routes of Abuse Matter – e.g., Opana ER

• Postmarketing data suggested that reformulation of Opana ER (never labeled with abuse-deterrent properties):
  – Decreased intranasal abuse, BUT
  – Caused a shift from snorting to injecting among individuals who abused the product
    – Seen in both poison control center and treatment center data
    – Consistent with spontaneous report patterns and information from outbreak investigations
    – Geographic clustering
  – Led to unintended consequences as injecting is more dangerous route (e.g., HIV/Hep C)
Exposure - Summary

• Exposure is multidimensional
  – Analgesic potency may not equal abuse potential
• Different measures of exposure can result in different effect estimates, especially relative effect estimates
• What patients take can vary substantially from what they receive
  – Varies by surgical procedure/medical condition and patient characteristics
  – Should inform prescribing guidelines and packaging solutions
• Difficult to identify “unnecessary” or “inappropriate” prescriptions
• Other patient opioid exposures not captured
• No exposure ascertainment for other individuals with access to the prescribed opioids
• Formulations matter, but are not captured in all data
• Routes of abuse matter, but aren’t always captured
Outcomes

(signal, descriptive, comparative)
Pathways to Misuse/Abuse of Prescription Drugs and Related Adverse Outcomes

Drug diversion

- Drug manufactured
- Drug distributed
- Drug prescribed/dispensed

Inappropriate use by patients

- Patient supply
- Drug diversion investigator survey data
- Drug seizure laboratory testing data
- Crowdsourced street price data

Patient use as prescribed

- Abuse
- Misuse
- Addiction
- Overdose
- Death

Outcome captured in...

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

Other serious AEs include: HIV, Hep C, endocarditis, TTP, arrhythmias

Illicitly manuf Rx drugs/heroin

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 and forensic toxicology data

National death certificate free text analysis

Crowdsourced street price data
Challenges in Using Healthcare Claims Data to Study Adverse Outcomes

• **Outcome ascertainment limited**
  – Mostly coded encounters within medical system (emergency department visits, hospitalizations, outpatient visits) – limited validation (overdose)
  – Usually limited detail on opioid substance or product involved in adverse outcomes
  – Does not capture intent well (e.g., misuse vs abuse vs. unintentional)
  – **Capture only subset of overdose deaths** – those occurring under treatment
Poor Capture of Meaningful Outcomes

• Misuse, abuse and opioid use disorder are often **covert**—not captured well in electronic healthcare data
  – No ICD-9 claims-based algorithms or EHR terms with good performance
  – Proxy outcomes of doctor/pharmacy shopping not yet shown to sufficiently predict actual misuse/abuse
  – Nonmedical outcomes such as interactions with the criminal justice system missing
• Route-specific outcomes are generally not available
• Quality of life and function not well captured
• Captures only a subset of overdoses
• More validation of outcomes needed
Ongoing Studies to Assess Electronic Health Care Data

Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records

Identifying and classifying opioid-related overdoses: A validation study

Using natural language processing of clinical text to enhance identification of opioid-related overdoses in electronic health records data
No Single Data Source Provides the Whole Picture

Healthcare Utilization Data
- Calling for advice on drug exposures; captures unknown spectrum of problems
- Seeking medical treatment—possibly incidental finding related to overdose/infection; captures unknown spectrum of problems

All misuse/abuse and related outcomes
- ED Visits/Hospital Admissions
- Addiction Treatment Admissions
- Mortality data
- Treatment Center Surveys
- National Health/School Surveys
- Internet/other Surveys
- Other data (FAERS, diversion data, street price)

Surveys
- Getting/being assessed for SUD/addiction treatment; captures more severe problems
- National samples; eligibility/sampling may capture less-severe problems
- Selected populations (internet panels, college students, patients)

ED, emergency department; SUD, substance use disorder
Sources of Outcome Data – Unique Pros & Cons

Poison Control Centers
- + Widespread catchment
- + Often product-specific information
- + May include individuals not otherwise represented in health care data
- Unknown percentage of events
- - Some identification of specific formulations
- - The most severe and fatal overdoses may not be captured

Surveys – General Population
- + Federal surveys are usually nationally representative
- + Capture wide range of misuse/abuse behavior
- + Can have specific populations (students)
- - Eligibility criteria may exclude those with more severe substance use disorders
- - Inability to capture product-level details such as formulation or route of abuse
- - Most are cross-sectional

Treatment Centers
- + Enriched “sentinel” population – can study new products
- + Details on products and formulations
- + Details on routes of abuse
- - Geographic and temporal variations limit ability for trending
- - Not nationally representative
- - Potential for product misclassification
- - Generally cross-sectional

Serial cross-sectional data do NOT equal longitudinal data
Data Linkages May Improve Capture of Exposure, Outcomes, and Confounders

• Prescription Drug Monitoring Programs (state-level)
• Overdose deaths
• Criminal justice data
• Substance use disorder treatment
  – Existing surveys
  – Information collected prospectively (e.g., patient-reported outcomes/patient input)
FDA is Funding Research to Enhance Linkages for Opioid Overdose Surveillance

• Grant to link several data streams in Connecticut
  – Office of the Chief Medical Examiner Cause of Death Data
  – Connecticut Hospital Association’s CHIME Data
  – Department of Correction Data
  – Prescription Drug Monitoring Program Data
  – Department of Mental Health and Addiction Services Data

• Contract to analyze linked data streams in Kentucky
  – PDMP, death certificates, autopsy reports, coroner investigations, and Medicaid claims data
Populations
(descriptive, comparative)
Geographic Variation

Revised May 2019

2017 Opioid-Involved Overdose Death Rates (per 100,000 people) ¹

Source: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state
Time Trends

Source: https://www.cdc.gov/drugoverdose/data/nonfatal/nonfatal-opioids.html
Opioids and Benzodiazepines – National Estimates and Ecological Associations

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

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<td>All opioid recipients</td>
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<td>0–17 years</td>
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<td>18–44 years</td>
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<td>45–64 years</td>
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<td>65+ years</td>
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<td>Chronic users</td>
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*Percentages were calculated using the midpoint of the calendar year.

*Percent of concomitant patterns, out of the total number of opioid recipients during a given calendar year.

Figure 2. Trends in opioid analgesic and benzodiazepine drug overdose deaths, U.S., 2004–2011.

Opioids and Benzodiazepines –
Local Data with Linkages

**Figure 5** Incidence rate ratios for overdose deaths involving opioid analgesics, by benzodiazepine prescription status. ...

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

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.

Case-cohort study among US veterans.

"4\textsuperscript{th} Wave" of Opioid Overdose Crisis

Overdose deaths, US

\textbf{Figure Source:} National Institute on Drug Abuse. \textbf{Data Source:} CDC Wonder.
Geographic Variation: Age-adjusted overdose death rates, 2017

Confounders
(\textit{comparative})
Other Efforts and Secular Trends

- Extremely difficult to isolate impact of REMS from many other interventions and secular trends since 2010
- Limited utility of comparator drugs—REMS could affect also

- Other opioid prescriber CE programs
- Prescription Drug Monitoring Programs
- Take-home Naloxone
- Cheap available heroin
- Drug take-back programs
- Prescribing guidelines
- Prior authorization and utilization review programs
- “Pill mill” laws and crackdowns
- Media coverage

Source: https://www.fda.gov/media/97531/download
This is What We Would Like

Exposure or Intervention → Outcome
This is the Reality – Confounders

Challenges and Future Directions
Challenges: DATA

• Data linkages to connect exposures with outcomes, measure confounders
  – Often collected in different systems (pharmacies vs medical examiners vs hospitals)
  – HHS working on this with national level data; FDA funding work in CT and KY

• Longitudinal data
  – Improve our understanding of trajectories from therapeutic use to addiction and overdose
    • Need prospective data, including data outside health care system
    • Do these differ by type of drug (opioids vs. stimulants)?
    • Identify key points for public health intervention
Challenges: METHODS

• Methods improvements/gaps in knowledge
  – What is appropriate denominator for measuring and comparing rates of adverse outcomes associated with a drug (e.g., misuse/abuse, addiction, overdose)?
  – What is more important for predicting misuse: potency/abuse potential of the molecule or availability of products in marketplace?
  – National vs. local populations: not the same problem everywhere
  – How to better understand growing polysubstance misuse, and the risks associated with specific pharmaceutical products?
    • E.g., are they contributing to the risk, or just innocent by-standers?