Challenges in Assessing Real World Use and Abuse of Pain Medicines

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U.S. Food and Drug Administration
Protecting and Promoting Public Health

Outline

- Measuring prescription opioid use
- Measuring prescription opioid abuse and its consequences
- FDA Collaborations for data development

Measuring Prescription Opioid Use

Drug Utilization Analyses: Prescription/Medical Claims Data

What we <u>can</u> measure

- Number of outpatient prescriptions
- Number of patients receiving outpatient prescriptions
  - Nationally estimated for outpatient retail pharmacy settings
  - Total, New, and Refill Rxs, strength, # of tablets, formulation
    - NDC codes
  - Demographics (age, gender, geography)
- Prescribing specialties (self-identified)
  - # of prescriptions by prescriber specialties

- Inpatient administrations (from hospital billing data)

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IR and ER/LA Opioid Analgesic Rxs
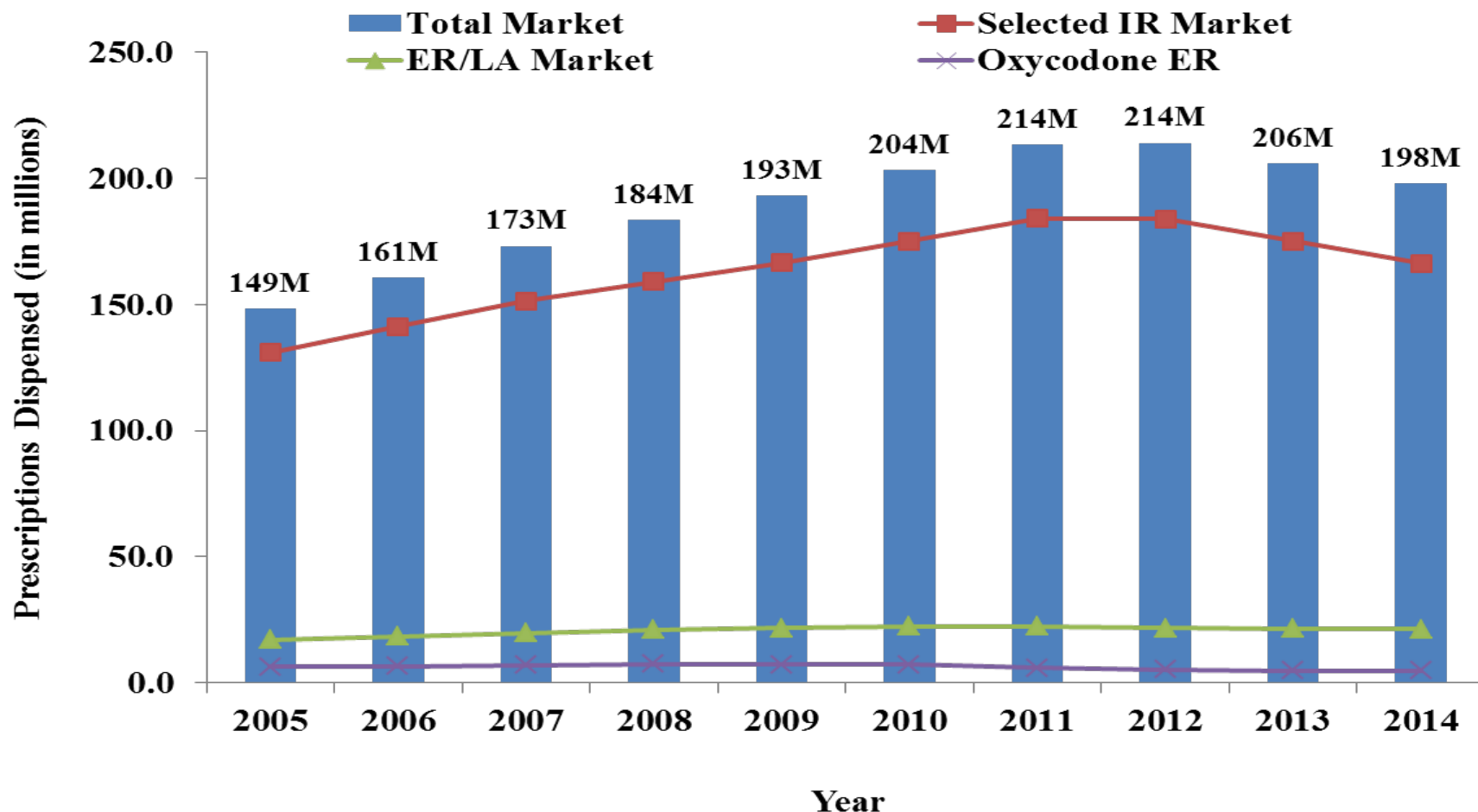
Nationally estimated number of prescriptions dispensed for selected IR and ER/LA opioid analgesics from U.S. outpatient retail pharmacies

Source: IMS Health, National Prescription Audit ™ Extracted May and August 2015

Drug Utilization Analyses: Prescription/Medical Claims Data

Challenging to measure

- Indication for treatment
- Switch analyses
  - Ex. ER/LA and IR opioids
- Concurrent use/co-prescribing
  - Ex. Opioids & benzodiazepines
- Acute/chronic use
- Medical history

What we **cannot directly** measure

- Abuse
- Illicitly acquired opioids
- Opioids dispensed in medical offices/clinics
- Appropriateness of therapy
- Patient access to Rx

Drug Utilization Analyses: Physician Survey Data

Indications for use (Prescribers' intent)

- Diagnoses associated with drug use from office-based physician surveys
  - ICD-9/ICD10 codes
  - Patient characteristics
- Cross-sectional in nature – can look at trends over time
- Only useful for drugs and indications with reasonable prevalence of use

Diagnoses Associated with Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics, January 2007-November 2011, Cumulative

	Hydrocodone Combination	Oxycodone Combination	Oxycodone IR	Morphine ER	Morphine IR
	N= 2,850,000	N= 1,406,000	N= 566,000	N= 2,618,000	N= 407,000
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	25%	20%	41%	68%	56%
Disease of Respiratory System (462-493)	21%	2%			
Fractures, Sprains, Contusions, Injuries (800-999)	19%	26%	8%	3%	4%
Follow up examinations	10%	14%	2%	4%	5%
Headaches and Nerve Pain (337-359)	3%	4%	38%	15%	20%
Fever and General Symptoms (780-789)	3%	4%	5%	2%	6%
Neoplasms (140-239)	2%	0%	5%	4%	0%
Disease of Genitourinary System (592-626)	2%	22%		0%	2%
Bacterial, Viral and Parasitic Infections (001-138)	1%	0%	0%	0%	0%
All others	13%	7%	2%	2%	7%

*Source: Encuity Research TreatmentAnswers™ , Extracted January 2012*

Measuring prescription opioid abuse and its consequences

Why is abuse different from traditional pharmacoepidemiology safety outcomes?

- Abuse occurs in patients and non-patients
  - Traditional data sources are specific to patients under medical care
- Outcomes associated with drug abuse are
  - Medical
  - Social
  - Legal
  - Occur in non-patients
  - Manifest in multiple settings
  - Traditional data sources do not capture full spectrum

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Pathways to the Abuse/Misuse of Prescription Drugs
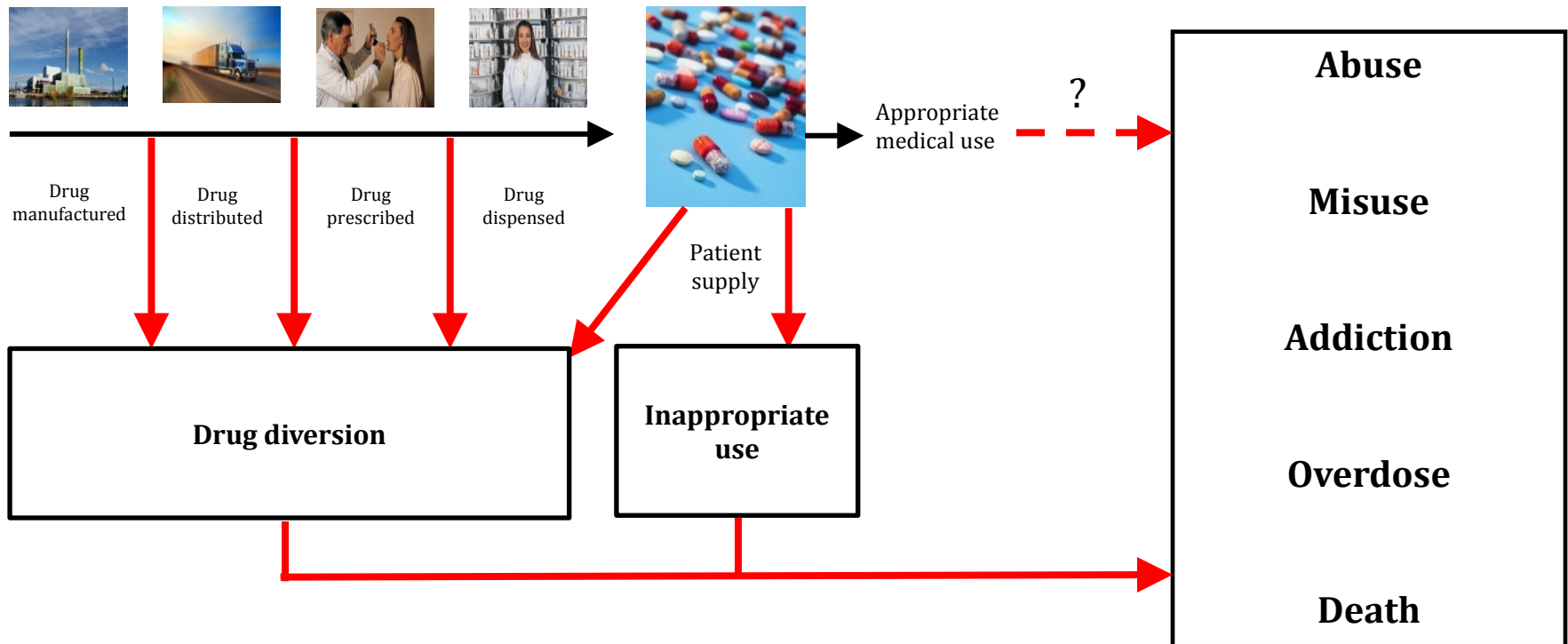
How do we assess abuse and compare *between* drug substance and formulations?

- No national abuse surveillance system for pharmaceutical products

- Abuse ratios ("abuse rates") are computed to estimate risk of abuse in the population and compare *between* products

- Numerators and denominators come from separate data sources

- These estimates are crude, but they are the only measures currently available

Numerators

Measures of misuse, abuse, addiction, overdose, death

Numerator Data Sources
Self-Reported Behavior of Abuse

- **National Survey on Drug Use and Health (NSDUH) Data**
  - Provides national estimates on the non-medical use of pain relievers
    - Estimates of lifetime as well as first time and past month use
    - Limited information by substance
- **Monitoring the Future (MTF) Data**
  - Provides data on drug-taking behaviors of school attending adolescents
  - Provides data specific to Vicodin® and OxyContin® - other prescription opioids treated as a class

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Numerator Data Sources
Morbidity

– **National Poison Data System (NPDS)**

- Calls to Poison Control Centers
- Substance, composition and formulation specific
  - Often missing/unavailable

– **Drug Abuse Warning Network (DAWN)**

- National Estimates of Drug Abuse Related Emergency Department visits
- Substance, composition and formulation specific
  - Often missing/unavailable
- Data collection ended in 2011

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Numerator Data Sources
Morbidity

- **Addiction Treatment Center data**
  - Convenience samples of addiction treatment centers that change over time
  - Standardized substance abuse assessments of individuals on admission to addiction treatment centers
  - Route of abuse available; can be product-specific
    - Misclassification of specific products abused can occur

- **Administrative claims data (eg, Sentinel System)**
  - Hospitalizations/ED visits for overdose/poisoning from medical claims
    - Codes not yet validated – work is underway
    - Opioid exposure information limited to that dispensed from pharmacies

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Numerator Data Sources
Mortality

– **National Vital Statistics data (NCHS)**

- ICD-10 codes
- Only methadone has unique code

– **State-specific medical examiner data**

- Florida (FDLE)

– **Administrative claims data (~Sentinel System)**

- Deaths outside of medical care are missed
- Requires linkage to other data sources (NDI)
- Opioid exposure information limited to that dispensed from pharmacies
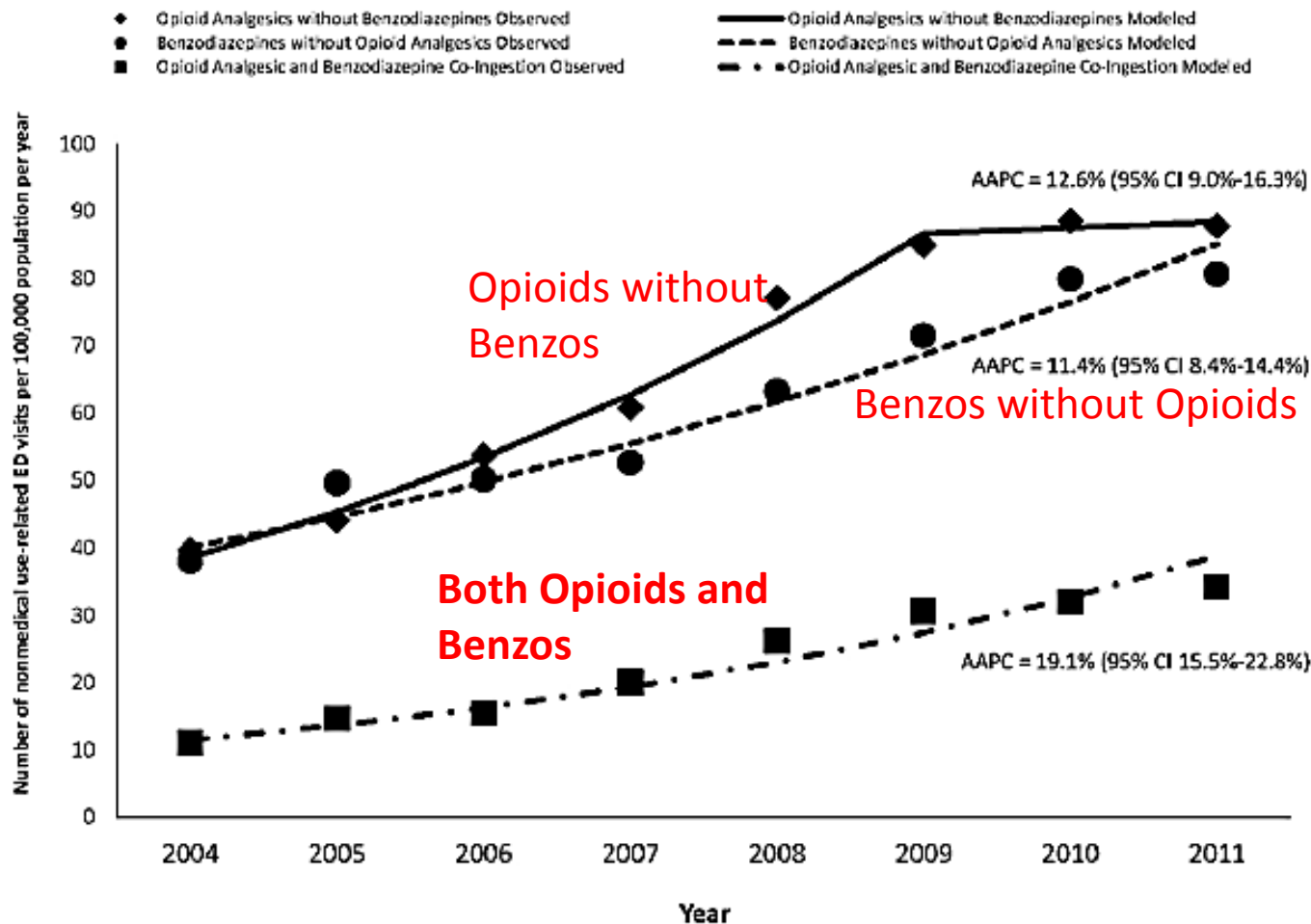
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Non-medical Use ED Visit Trends

Figure 1. Trends in opioid analgesic and benzodiazepine nonmedical use-related emergency department visits, U.S., 2004–2011.

AAPC = Average annual percent change
Jones CM and McAninch JK, "Emergency Department Visits and Overdose Deaths from Combined Use of Opioids and Benzodiazepines," Am J Prev Med, October 2015
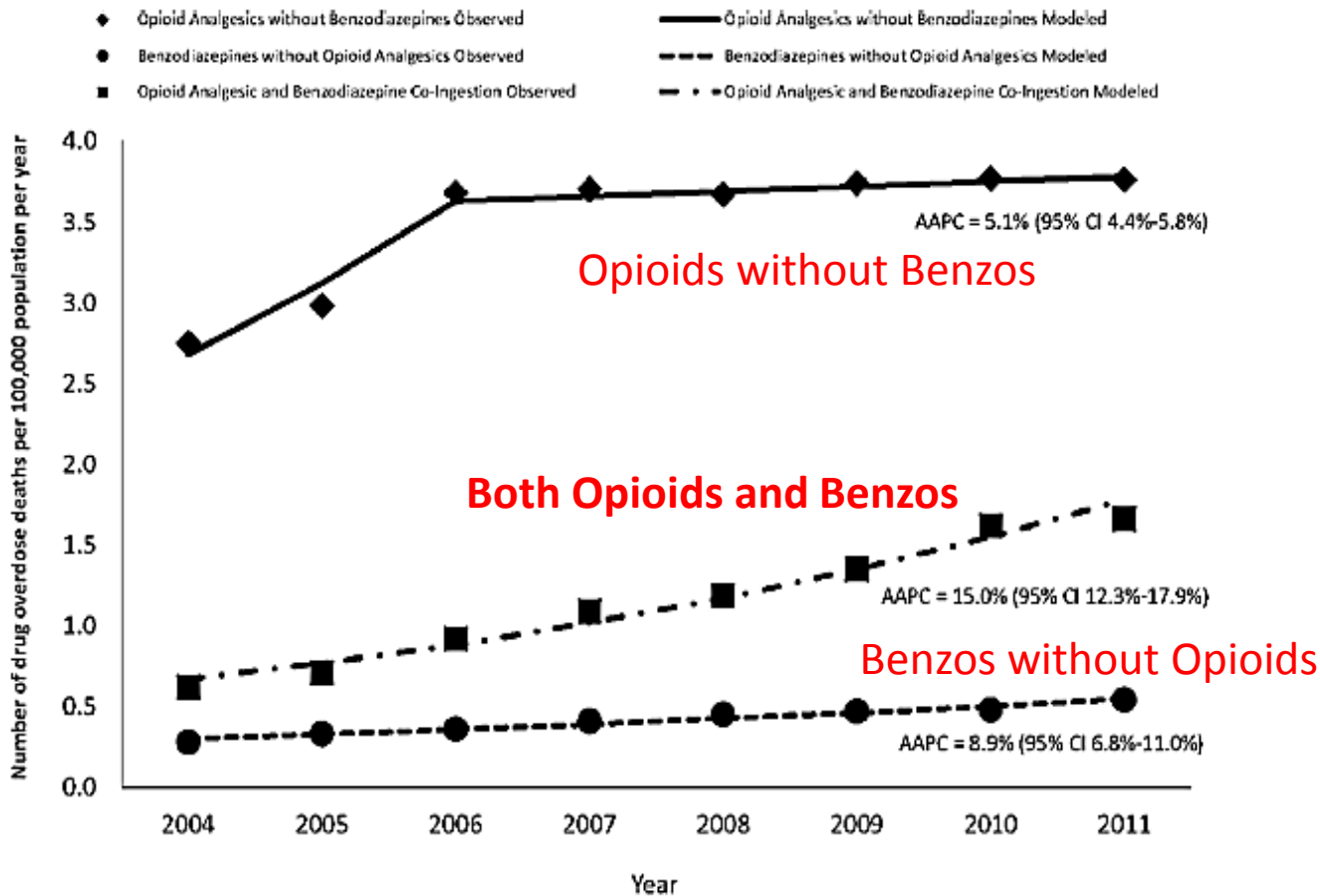
Overdose Mortality Trends

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

*AAPC = Average annual percent change
Jones CM and McAninch JK, "Emergency Department Visits and Overdose Deaths from Combined Use of Opioids and Benzodiazepines," Am J Prev Med, October 2015*

Numerators are limited

- The majority of the existing data sources **do not** provide information on:

    - specific product

    - composition (single ingredient vs. combination product)

    - formulation (immediate release vs. extended release)

Denominators – which one?

- Total U.S. population
- Total number of prescriptions
- Patient-days of Therapy
- Amount of Substance Distributed (in kilograms of the salt)
- Total number of patients receiving a prescription
- Total number of tablets dispensed ("extended units")
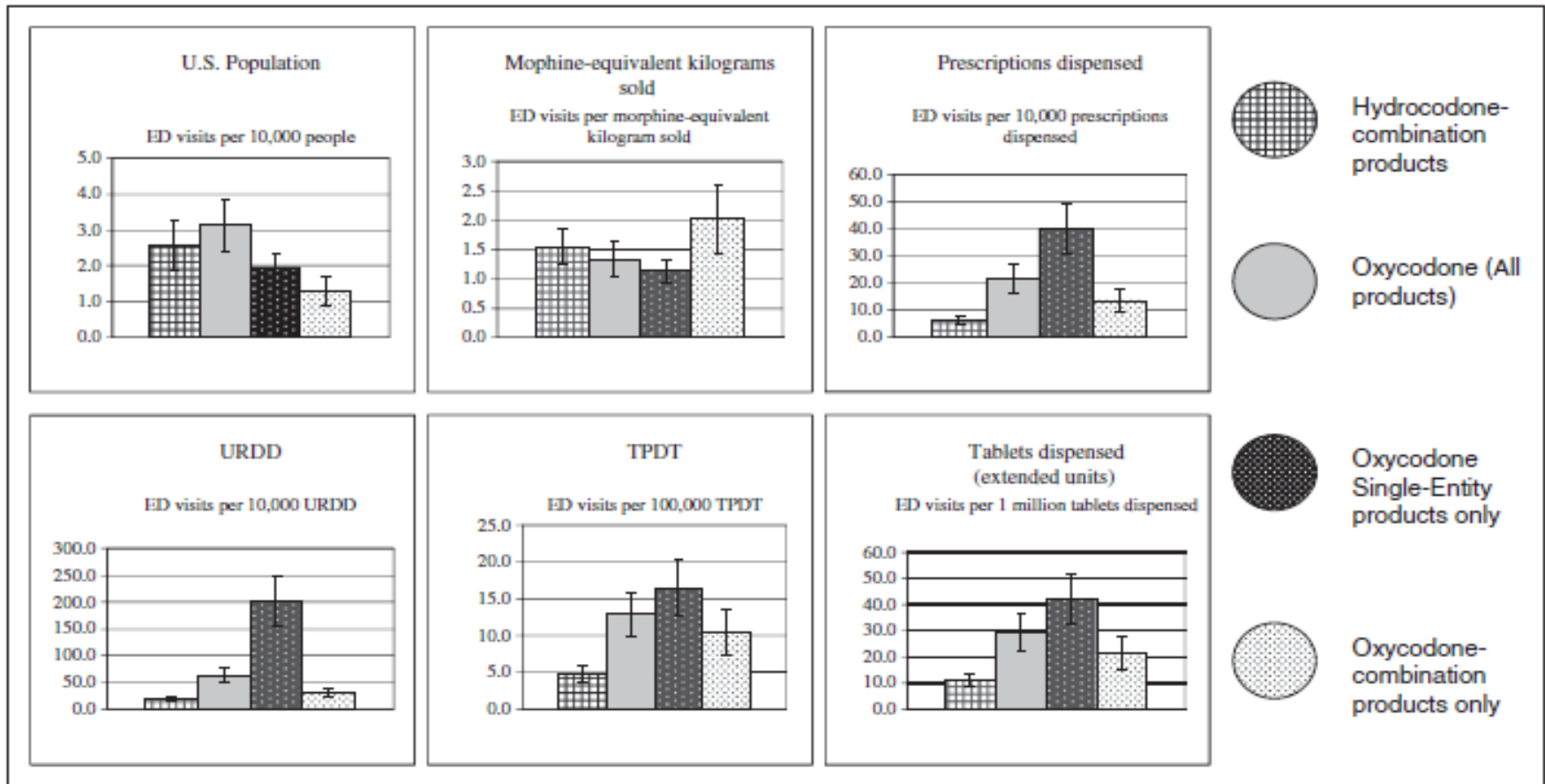
Impact of using different denominators

Figure 1. Variability in ARs for select opioid product types. The variation seen in ARs for 2007 using Drug Abuse Warning Network (DAWN) All Misuse/Abuse emergency department (ED) visit data as the numerator, and all available denominators. The error bars represent the 95% confidence intervals around the DAWN estimate. All drug utilization data were obtained from IMS Health, Vector One® (Danbury, CT, USA): National, Total Patient Tracker, and National Sales Perspective™ databases. Population figures came from U.S. census data for 2007. Morphine-equivalent conversions were obtained from a standard analgesic conversion table.[61] This figure provides evidence that choosing appropriate denominators is a critical consideration when comparing between some opioid product types

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Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. Pharmacoepidemiol Drug Saf. 2014 Dec;23(12):1227-37

Methodological Challenges:
Measuring abuse over time and across products

- Questions about utilization adjustment and comparators

- Dynamic and non-random study populations

- Incorporating secular trends (regulatory actions, publicity, enforcement activities)

- Inferring individual risk from ecologic analyses

- Generalizability of results from sub-national populations

So…how do we interpret these imperfect data and evolving methods?

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A Framework for Interpretation

- Despite the many challenges, these studies are needed to inform regulatory and policy decisions

- Abuse-deterrent medications and mechanisms need to be evaluated in real-world settings

- Often have multiple studies with varying approaches and populations; results must be understood as a coherent unit

Going "back to basics" – Hill's principles for causal inference

Focusing on the following:

– Temporality

– Effect Size

– Specificity

– Consistency

– Alternative Explanations

FDA collaborations for data development

The Ideal Data System would be…

- Flexible and expandable beyond opioids
- Timely, with data updates every 6 months
- Able to correctly and reliably distinguish brands, formulations and routes of abuse
- Able to provide national and regional estimates
- Composed of complementary components
  - Surveillance (e.g., encounters, clinical outcomes)
  - Quantification (ability to track over time)
  - Impact (linkage with law enforcement, other data)
- But does not currently exist!

Prescription Behavior Surveillance System (PBSS)

- Uses data from participating states' prescription drug monitoring programs (PDMPs)

- Measure trends in controlled substance prescribing and dispensing

- Develop indicators of medical and non-medical use, diversion, and inappropriate prescribing and dispensing

- Currently 15 states are enrolled in the PBSS

- Data are currently available via data portal

National Hospital Care Survey (NHCS run by NCHS)

- Enrollment underway to collect emergency department (ED) data from hospitals participating in the NCHS system

- Currently have ~85 hospitals for ED data

- 2015 national estimates, expected in early 2017

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NEISS-CADES expansion

- Currently 61 hospitals (to date) providing ED data for national projections of <u>drug-related</u> injuries

- In 2015, expansion efforts to train coders to include ED visits that were the result of drug-abuse and self-harm

- In 2016, first full year of data collection on drug abuse cases

- Drug abuse related ED visits expected to be available approximately Nov/Dec 2017

Postmarketing Required Studies

- Manufacturers of ER/LA opioid analgesics have been required to conduct 11 studies
  - 10 are observational studies
  - Assess risk for misuse, abuse, addiction, overdose and death among patients prescribed ER/LA opioid analgesics
  - Validation of multiple outcomes
 - Foundation for further research

Death certificates – literal data

- CDC/FDA developing capability to identify specific drug names from literal text on death certificates
- Will provide capability to differentiate between opioids when information provided
- Limitations of death certificates in general
  - Lag time
  - Inconsistent ascertainment of drugs in deaths

Abuse/Misuse-Related Outcomes and Data Sources
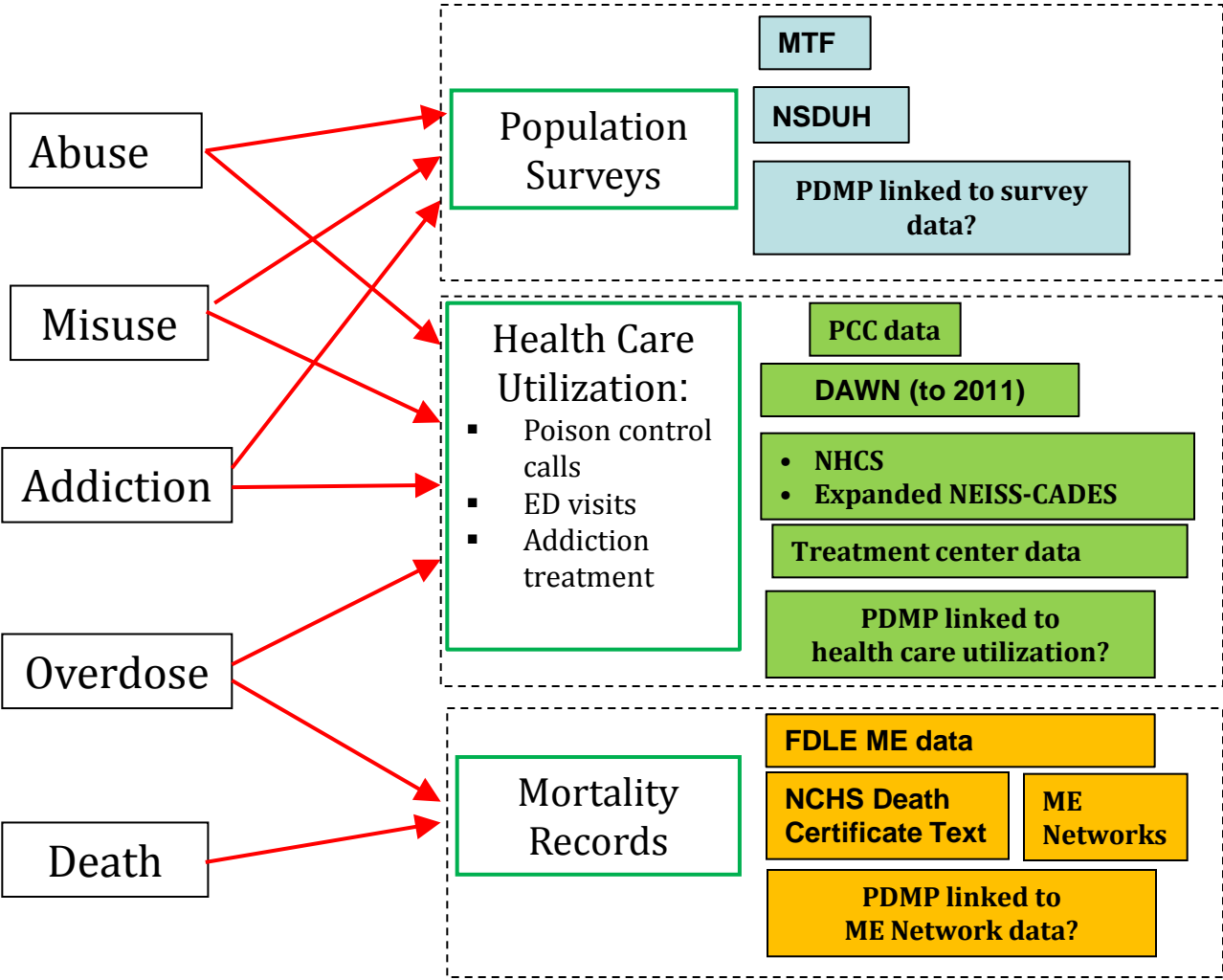
Key areas for research

– Defining and validating key concepts (e.g. abuse, misuse, prescription drug addiction, overdose, doctor shopping)

– Distinguishing aberrant patient behavior from legitimate care-seeking

– Improved insight into pathway from legitimate use to substance abuse and addiction

Questions?