Designs That Assess Exposure and Outcome in the Same Individuals Over Time

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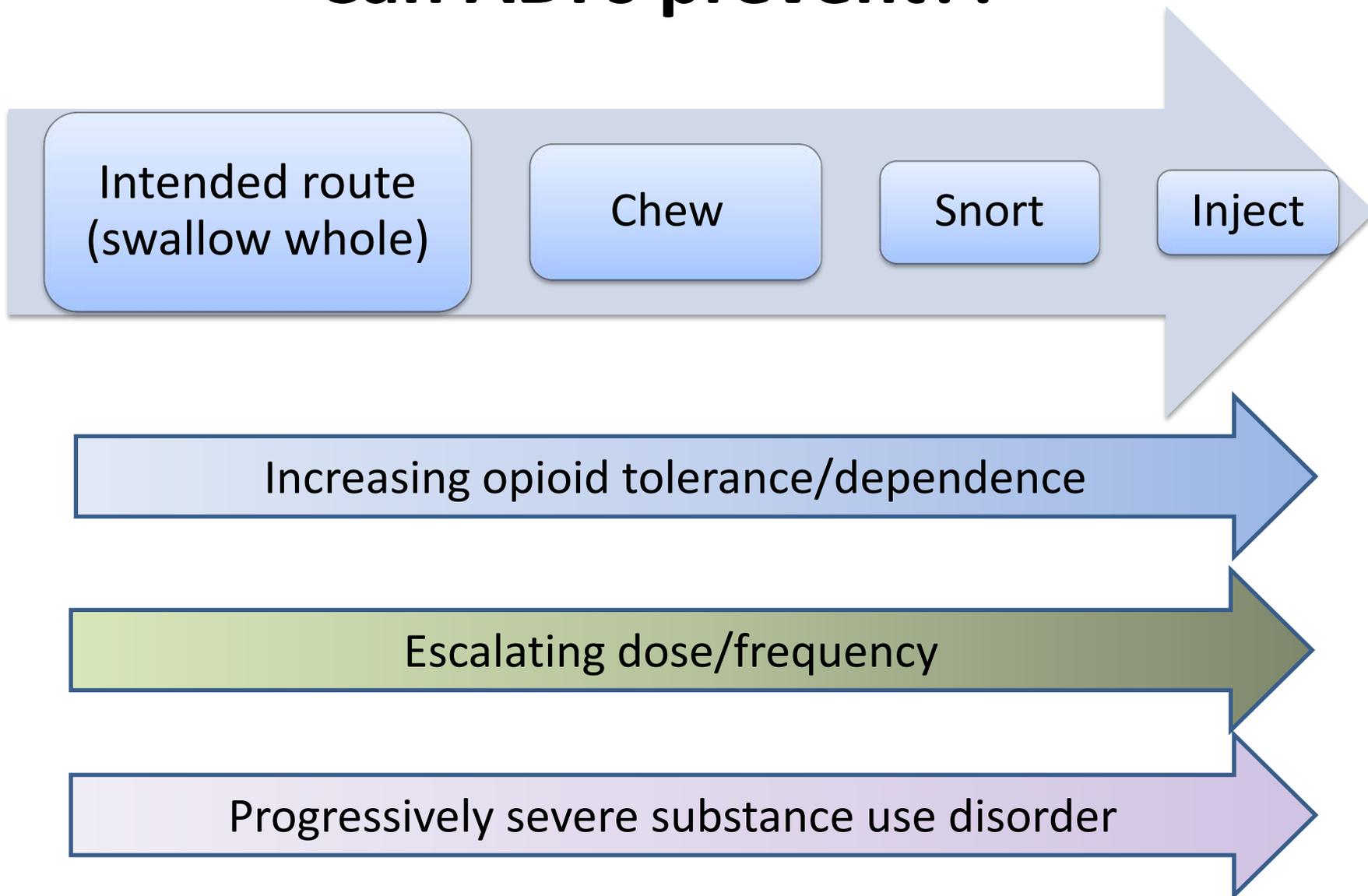US Food and Drug Administration

Overview

- Causal question

- Summary of challenges

- Study designs with examples
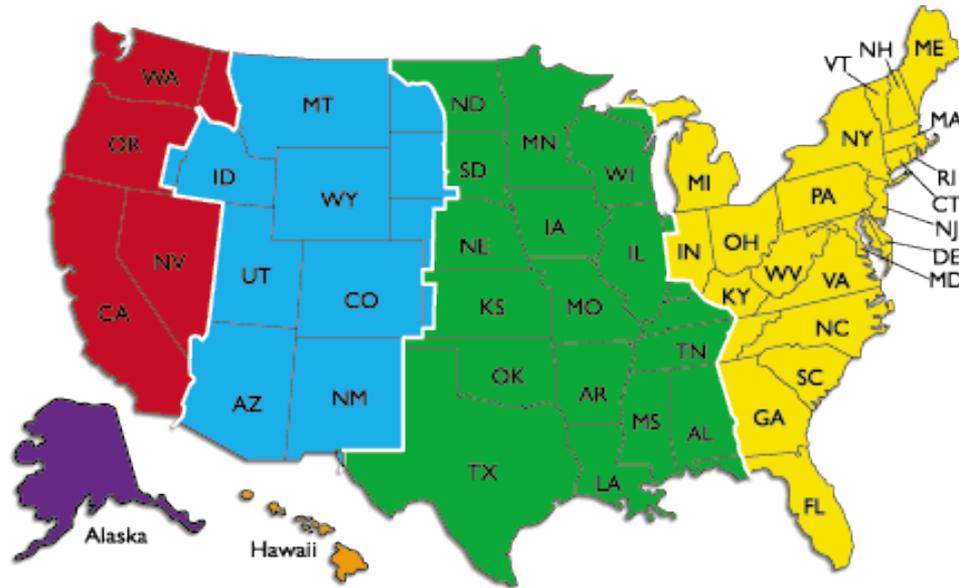
- Discussion questions

CAUSAL QUESTION

Progression of Opioid Misuse/Abuse **Can ADFs prevent??**

FDA

| Intended route (swallow whole) | Chew | Snort | Inject |

→ Increasing opioid tolerance/dependence

→ Escalating dose/frequency

→ Progressively severe substance use disorder

2009

2012

Pacific   Mountain   Central   Eastern

TIME

CHALLENGES

Summary of Challenges

- Sampling the relevant populations for the study question and achieving appropriate sample size

- Adequately capturing confounders

- Choosing appropriate comparator(s)

- Accurately capturing exposure (prescribed and obtained from other sources) and outcomes

- Choosing study design to balance efficiency/resources with strong causal evidence

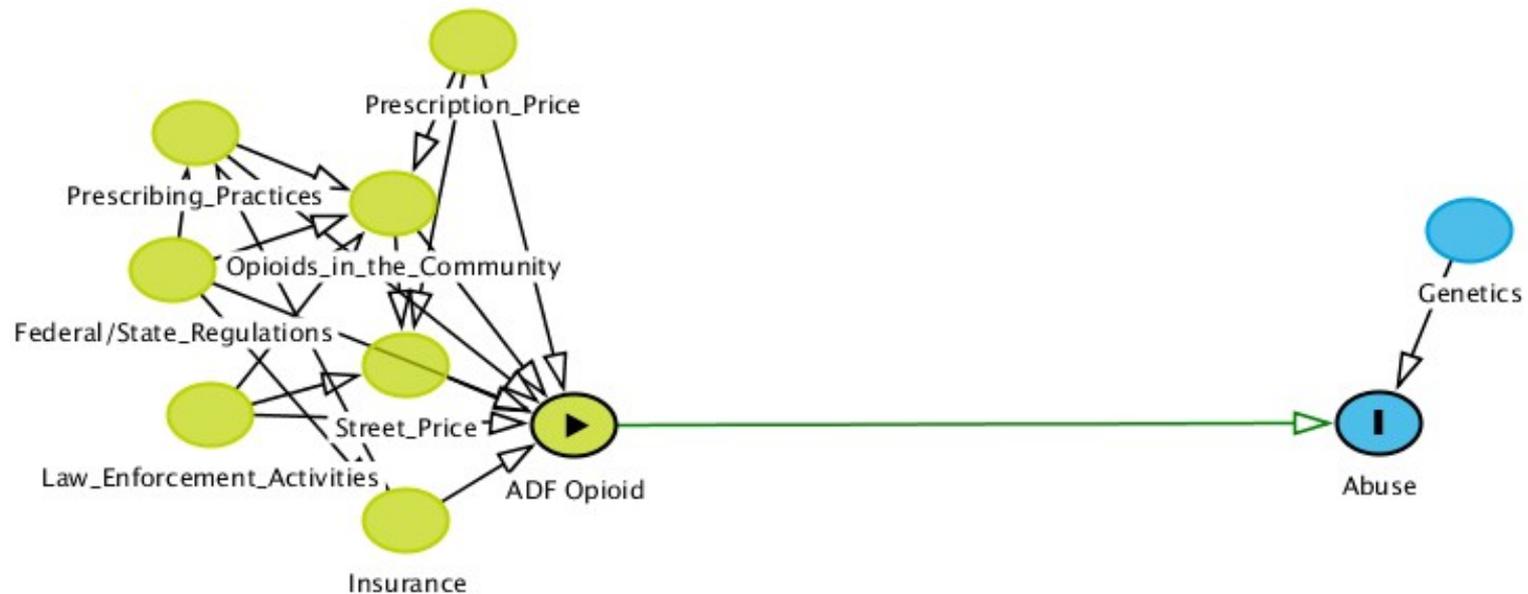# Sampling Relevant Populations

OUD, Opioid Use Disorder
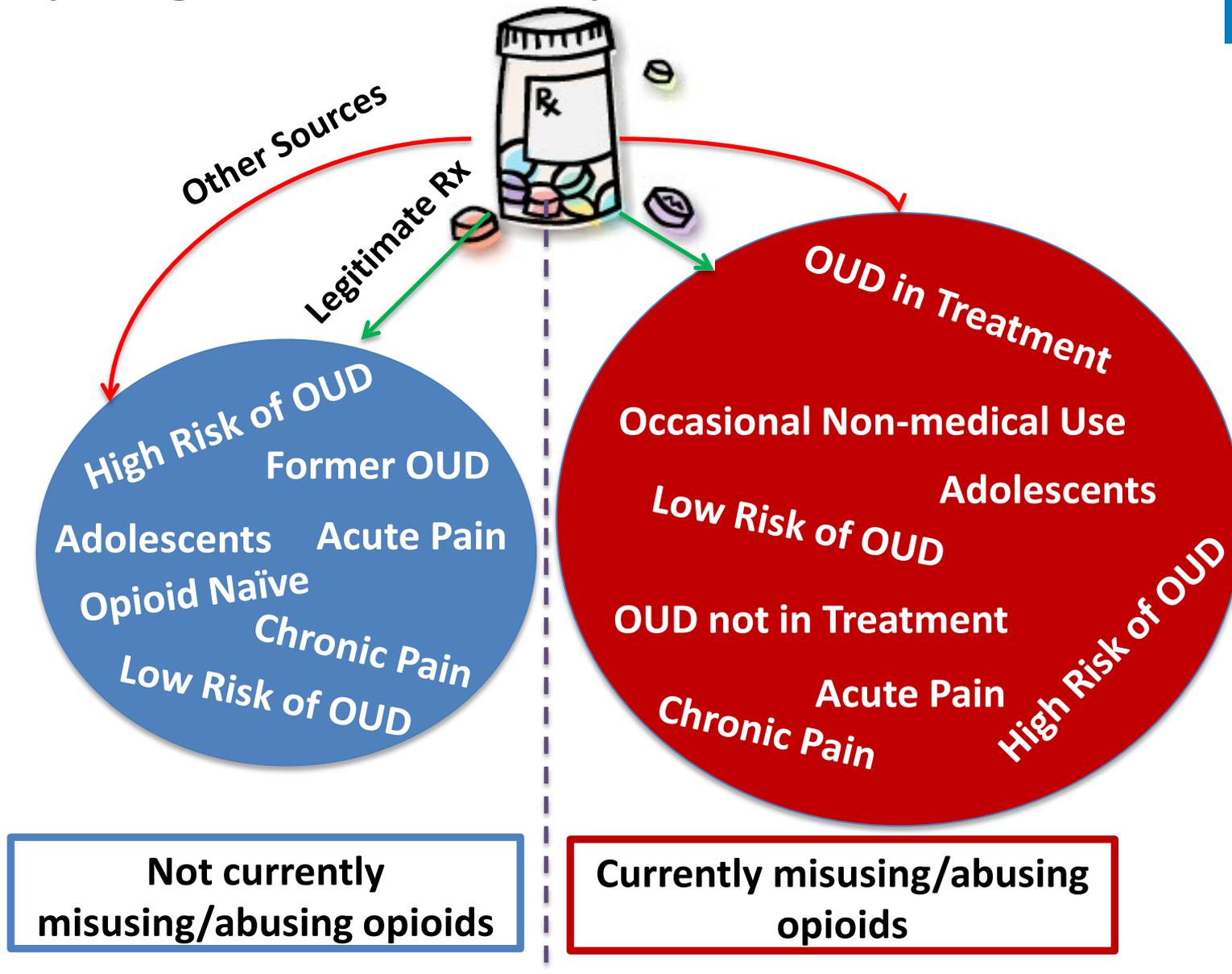
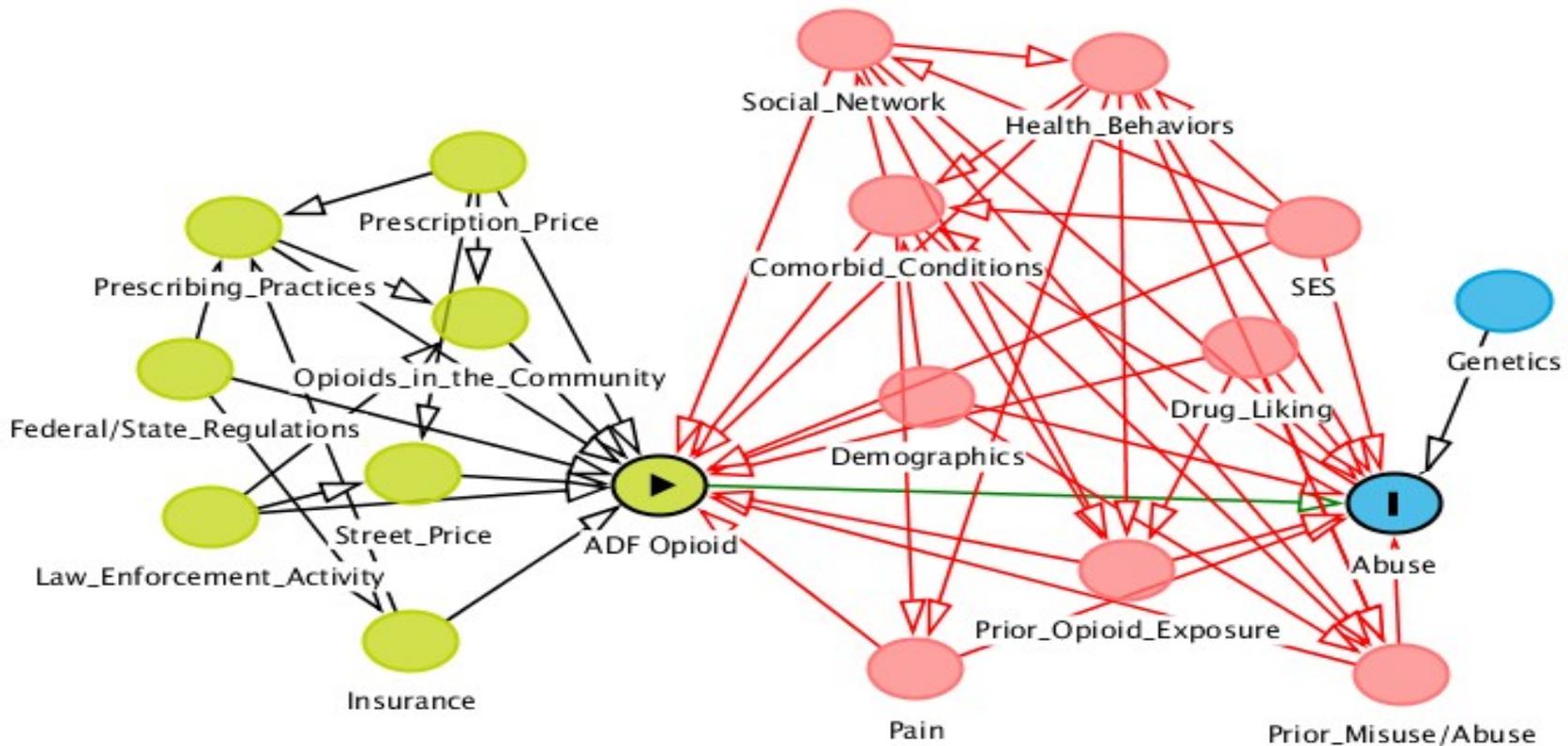# Confounders

Confounders

Generated using DAGity. Johannes Textor, Juliane Hardt, and Sven Knüppel. Dagitty: A graphical tool for analyzing causal diagrams. Epidemiology, 22(5):745, 2011.

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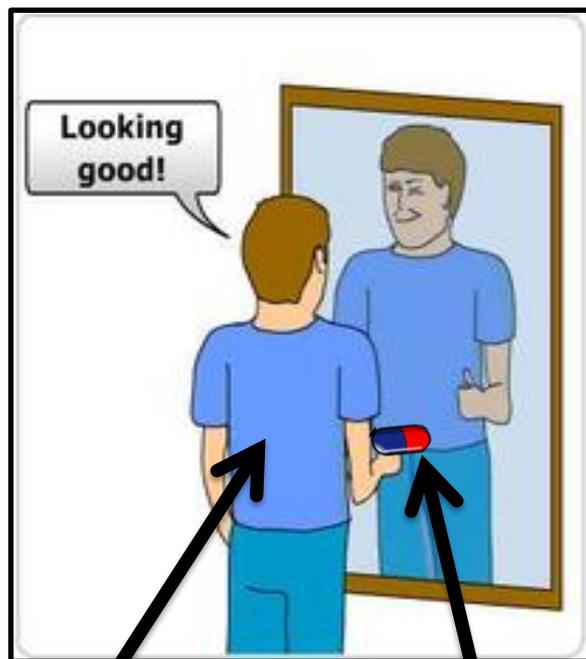# Confounders

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Choosing Comparators

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Looking good!

Person characteristics (e.g., indication, prior abuse, SES)

Drug characteristics (e.g., active ingredient, formulation, pharmacology, likeability)

Counterfactual Condition

- **Opioid product(s) without abuse-deterrent properties?**
- **Others?**

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Capturing Exposures and Outcomes

- Exposures
  - Need to capture both *prescribed drugs* and *drugs obtained from other sources at the* **product-specific** *level*

- Outcomes
  - Timing and type of outcome
  - Operationalizing "hard" vs "soft" outcomes
  - **Route-specific abuse**

- Healthcare claims as example
  - Exposures: prescribed drugs only, often missing cash payments, days supply of a prescription may not equal true use
  - Outcomes: algorithms with poor accuracy, especially for "soft" outcomes like misuse/abuse, and no way to capture route of abuse

STUDY DESIGNS

A Word on Examples

- Example for various types of individual-level studies to help spark ideas

- Some examples of general opioid exposures or non-abuse outcomes that may be useful for assessing ADF opioids

- Not endorsing or critiquing these studies

- We're here to get your thoughts

Nested Case-Control

- Purpose: Assessed risk of road trauma related to recent opioid dose in Ontario, Canada using healthcare claims data sources[1]

- Nested within population of patients with ≥ 1 opioid claim

- Cases with first ED visit for road trauma during study period compared to matched controls with no ED visit for road trauma using incidence density sampling

- Both cases and controls had an opioid prescription overlapping the index date and the average daily doses were compared

- General design strengths: Same as retrospective cohort using claims

- General design limitations: Same as retrospective cohort using claims plus careful sampling of controls needed to ensure similar risk for outcome, and techniques like propensity scores to control for confounding not yet established

1. Gomes T., et al. JAMA Intern Med 2013; 173: 196-201.

Outbreak Investigation

- Purpose: assessed exposures linked to an initial outbreak of 11 HIV infected patients in Scott County, Indiana in 2015[2, 3]

- From Nov 2014-Nov 2015 they identified 181 cases with HIV infection; 87.8% reported injecting ER oxymorphone (Opana ER, Endo Pharmaceuticals)

- After matching 287 close contacts without HIV, number of times named as a syringe-sharing partner was associated with HIV infection

- Used questionnaires about syringe-sharing, sexual partners, and other information; conducted phylogenetic analysis and HIV testing of contacts

- General design strengths: Good for rare outcomes that come to medical attention

- General design limitations: Smaller sample sizes, generalizability concerns, careful selection of control group needed, and exposure information is collected after case leading to potential accuracy issues

2. Conrad C., et al. MMWR 2015; 64: 443-4., 3. Peters, PJ, et al. NEJM 2016; 375:229-39.

Retrospective Cohort

- <u>Purpose:</u> one of FDA-required extended-release/long-acting (ER/LA) PMR studies—will assess incidence of overdose and death in patients newly prescribed an ER/LA opioid

- Exposure assessed via claims for prescription fills

- Outcome assessed via claims data algorithms and linkage to National Death Index (NDI) mortality data

- <u>General design strengths:</u> Large sample sizes and accurate product information for prescribed opioids paid through insurance

- <u>General design limitations:</u> No cash or outside sources of exposure, limited accuracy for outcomes based only on claims, and poor capture of potential confounders

Historical Cohort

- Purpose: assessed rates of doctor shopping for OxyContin and comparators before and after reformulation in IMS LRx claims data[4]

- Doctor shopping for a specific product defined as ≥2 prescribers and ≥3 pharmacies in 6-month period

- OxyContin doctor shopping relative risk was risk in cohort of patients after the reformulation (Jan 2011-June 2013) vs risk in cohort of patients before reformulation (July 2009-Jun 2010).

- Ratio of relative risks generated for Oxycontin vs comparators

- General design strengths and limitations: Same as retrospective cohort plus limitation of time-related biases between two cohorts

4. Chilcoat H.D., et al. Drug Alcohol Depend 2016; 165: 221-8.

Prospective Cohort

- Purpose: examined impact of April 2014 introduction of reformulated OxyContin

- The National Opioid Medications Abuse Deterrence (NOMAD) study[5,6] followed 606 patients who regularly misused pharmaceutical opioids in Australia

- Questionnaires collected data at multiple time-points on route of abuse for pharmaceutical and illicit opioids, overdose, injection-related injury, and others

- General design strengths: can capture opioids from both prescribed and other sources, can collect rich information on confounders, can use standardized definition of outcomes

- General design limitations: smaller sample sizes and concerns about self-reported exposures, especially at the product-level

5. Degehardt L., et al. Addiction 2014; 110: 226-237., 6. Degenhardt L., et al. Drug Alcohol Depend 2015; 151: 56-67.

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DISCUSSION

Discussion Question #1

Discuss which populations are the highest priority targets for assessing the effectiveness and safety of abuse-deterrent products.

Discussion Question #2

Discuss which potential confounders or modifying factors are most important for evaluating the effectiveness and safety of ADF opioids in studies assessing exposure and outcome in the same individual over time.

– Consider patient-level, provider-level, and policy-level factors with respect to specific outcomes

Discussion Question #3

Discuss the most important characteristics of comparators for evaluating the effectiveness and safety of ADF opioids in studies assessing exposure and outcome in the same individual over time.

- Consider:
  - properties of the drug (e.g., active ingredient, formulation, pharmacology)
  - characteristics of patients who use the drug (e.g., indication, comorbidities, SES)

Discussion Question #4

Discuss which study design(s) may be the most useful for future studies of the effectiveness and safety of ADF opioids.

- Consider:
  - Cohort (e.g., small prospective, retrospective, historical)
  - Case-control (e.g., nested case control and outbreak investigations)
  - Others?
  - Weigh resource intensity and time for study conduct against strength of causal evidence (e.g., misclassification, availability of confounders, temporality)

Discussion Question #5

Discuss the feasibility and importance of assessing unintended/secondary consequences of ADF opioids (e.g., shifting abuse to other opioids, including heroin)?