Pharmacoepidemiologic Research on Drugs of Abuse

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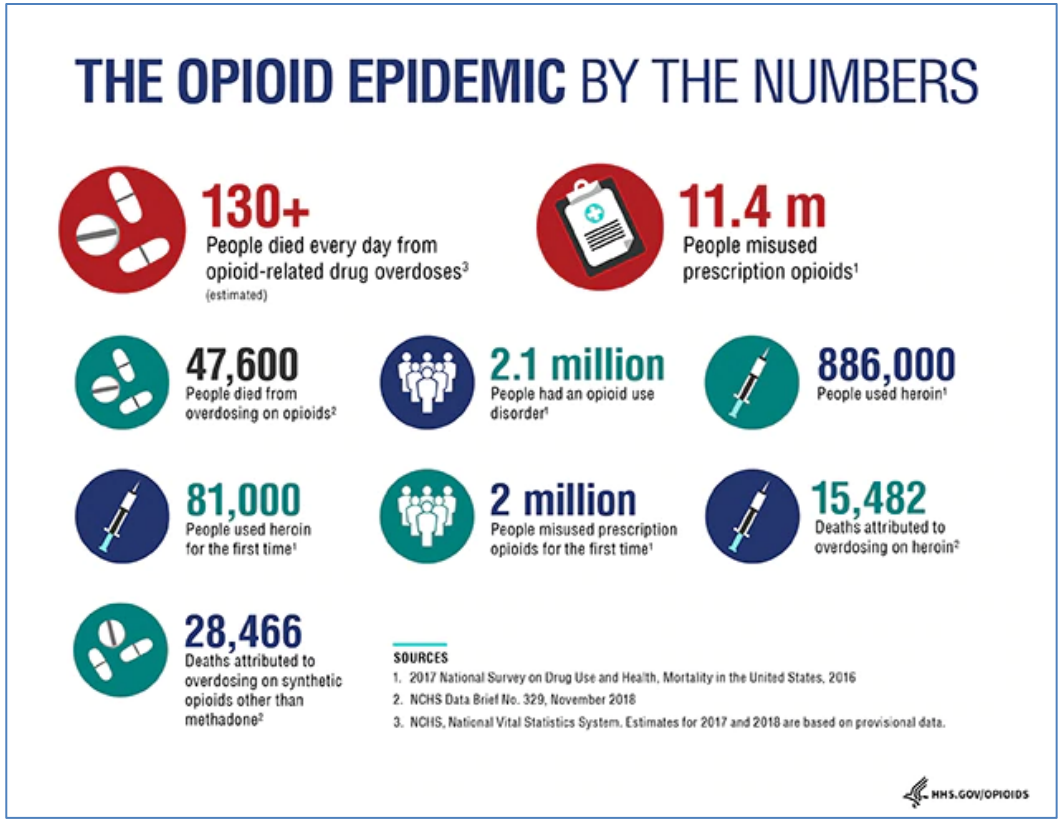
The views expressed in this presentation are those of the presenter and not necessarily those of the US Food and Drug Administration.

No conflicts of interest to disclose.

The Opioid Crisis and Pharmacoepidemiology

- A societal problem
- Misuse, opioid use disorder, abuse, overdose and death are <u>drug safety issues</u>
- 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

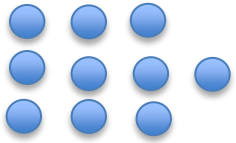
What is the question?

Data sources and approaches depend on the question

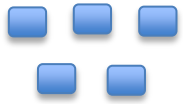
1. **Signal detection and assessment**
   - Do we see emerging reports of abuse with drug X?
   - Are there new/unrecognized AEs associated with drug X under the context of abuse?
2. **Descriptive population data on abuse and related outcomes**
   - Scope (public health burden)
   - Trends (getting better 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*)

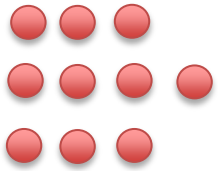
Population Measures of Exposure



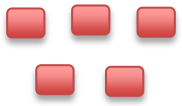
Morphine sulfate extended release – 10 mg



Morphine sulfate extended release – 200 mg



Oxycodone hydrochloride – 5 mg



Oxycodone hydrochloride extended release – 80 mg

Number of Rx	Number of Tablets	Total mg content	Number of MMEs
1	10	100	100
1	5	1000	1000
1	10	50	75
1	5	400	600

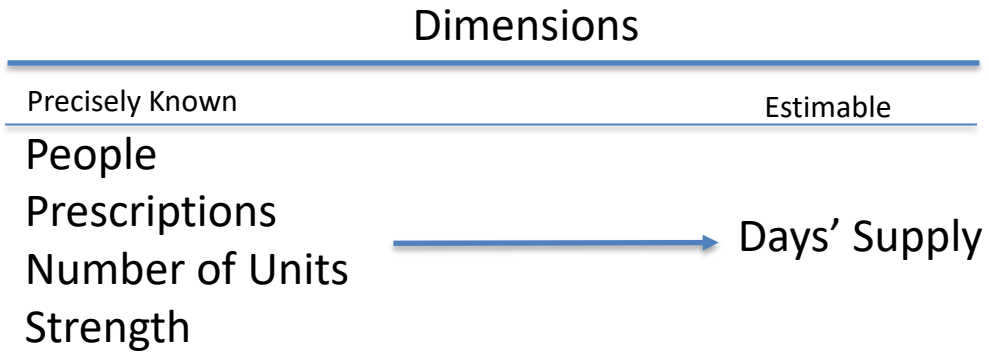
Opioid Exposure Measures are Multidimensional

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

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total Rx	145 M	154 M	166 M	178 M	194 M	199 M	208 M	219 M	230 M	223 M	235 M	244 M	250 M	257 M	258 M	260 M	252 M	244 M	228 M
Brand Rx	46 M	46 M	48 M	51 M	52 M	48 M	41 M	38 M	26 M	16 M	14 M	16 M	18 M	17 M	17 M	14 M	12 M	12 M	9 M
Generic Rx	99 M	108 M	118 M	127 M	142 M	150 M	166 M	181 M	205 M	207 M	221 M	228 M	232 M	240 M	241 M	246 M	239 M	232 M	218 M
Rx per 100 population	53	56	59	63	68	69	72	75	78	75	78	80	81	83	83	83	80	77	71
MME	70 B	79 B	87 B	105 B	121 B	134 B	151 B	167 B	183 B	181 B	199 B	215 B	227 B	244 B	240 B	234 B	224 B	217 B	206 B
MME per Rx	486	511	524	589	621	675	725	763	793	813	848	882	909	950	932	899	890	888	905
MME per capita	256	284	311	373	424	467	520	572	618	608	662	707	740	791	771	745	708	680	641

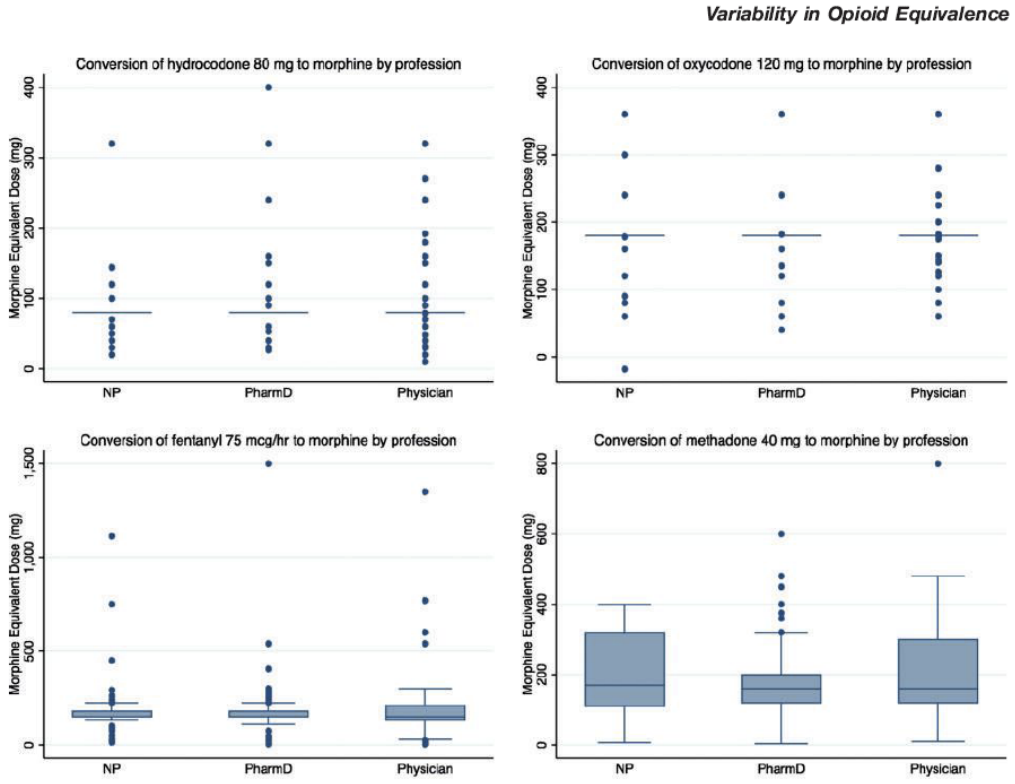
Estimates were derived from total U.S. Census population projections and estimates and IQVIA, National Prescription Audit. Prescriptions dispensed per 100 persons adjusted to the U.S. Census population. Brand: all trade name products including brand and branded generic products. Excludes injectable formulations,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

Source: Chai G, et al. Anesthesiology 2018;128:953-966



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



Source: Rennick A, Atkinson T, Cimino NM, Strassels SA, McPherson ML, Fudin J (2015) Variability in Opioid Equivalence Calculations. Pain Medicine

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

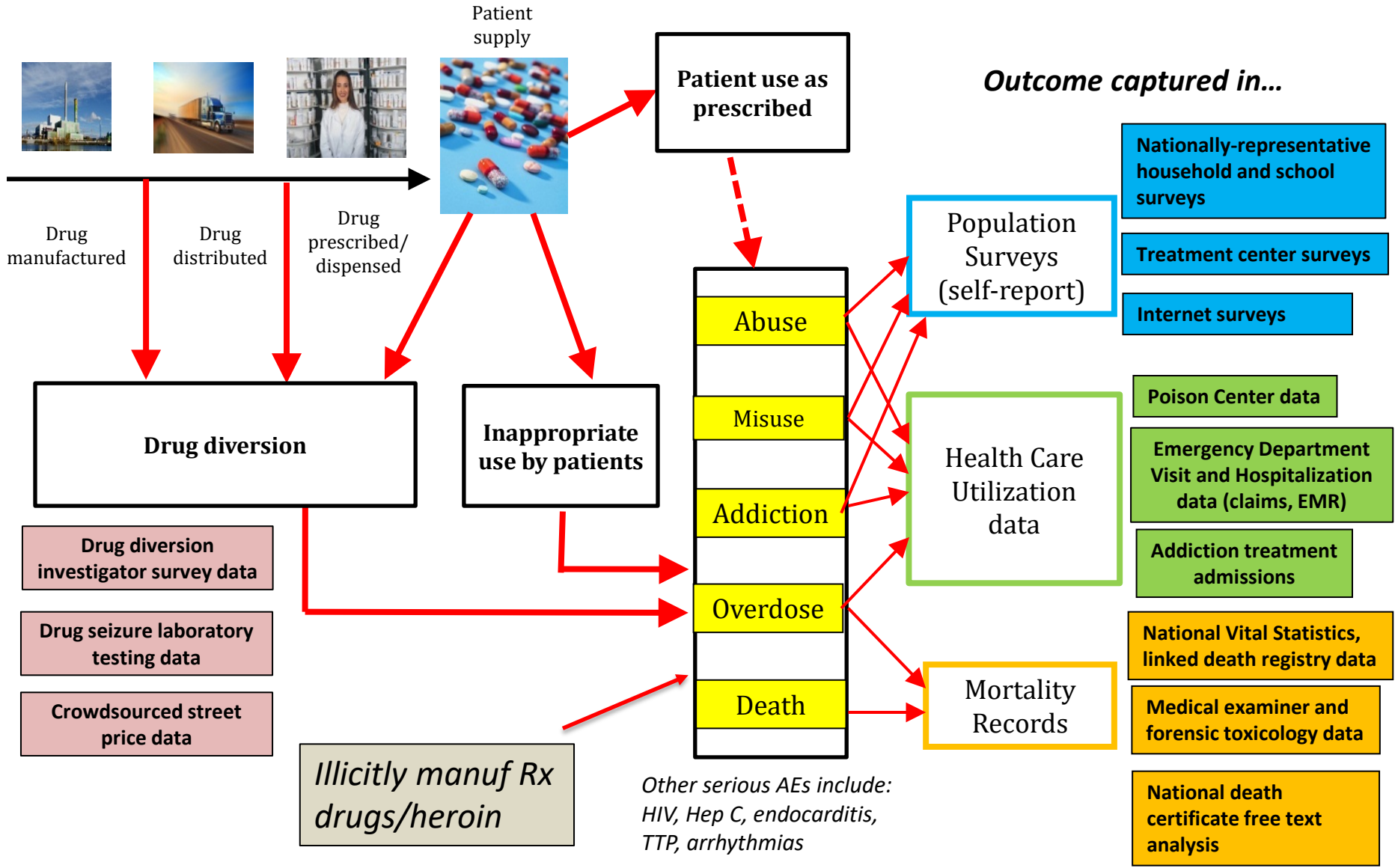
- Postmarketing data suggested that reformulation of Opana ER (never labeled with abuse-deterrent properties):
  - Decreased intranasal abuse, BUT
  - Caused a shift from snorting to injecting among individuals who abused the product
    - Seen in both poison control center and treatment center data
    - 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



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

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; 26: 509–517
Published online 10 January 2017 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.4157

ORIGINAL REPORT

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

Carla A. Green[1*], Nancy A. Perrin[1], Shannon L. Janoff[1], Cynthia I. Campbell[2], Howard D. Chilcoat[3] and Paul M. Coplan[4]

ORIGINAL REPORT

WILEY

Identifying and classifying opioid-related overdoses: A validation study

Carla A. Green[1] | Nancy A. Perrin[1,9] | Brian Hazlehurst[1] | Shannon L. Janoff[1] | Angela DeVeaugh-Geiss[2] | David S. Carrell[4] | Carlos G. Grijalva[5] | Caihua Liang[6,7] | Cheryl L. Enger[6,7] | Paul M. Coplan[3,8]

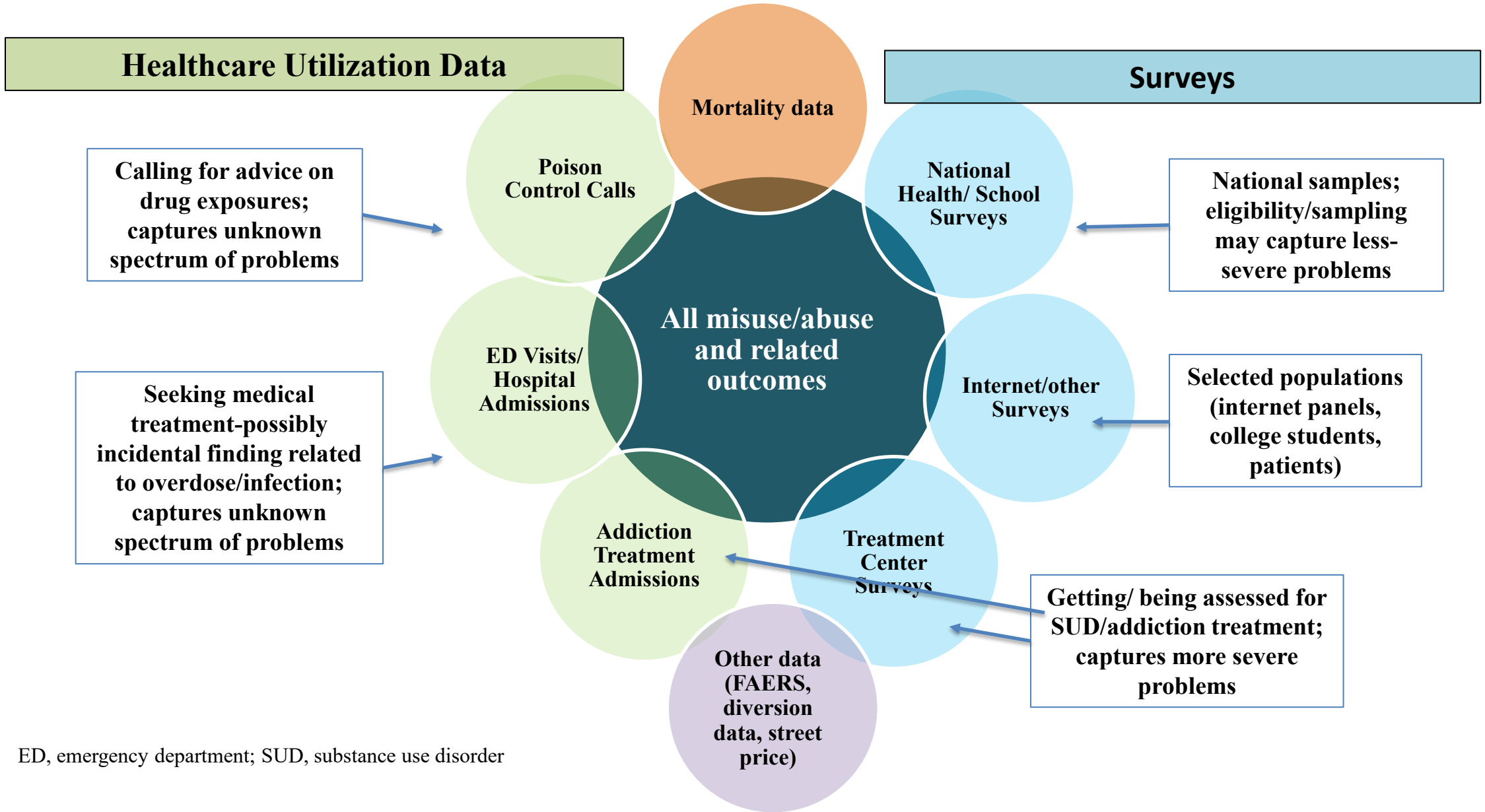
ORIGINAL REPORT

WILEY

Using natural language processing of clinical text to enhance identification of opioid-related overdoses in electronic health records data

Brian Hazlehurst[1] | Carla A. Green[1] | Nancy A. Perrin[1] | John Brandes[1] | David S. Carrell[2] | Andrew Baer[3] | Angela DeVeaugh-Geiss[4] | Paul M. Coplan[4,5]

No Single Data Source Provides the Whole Picture



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

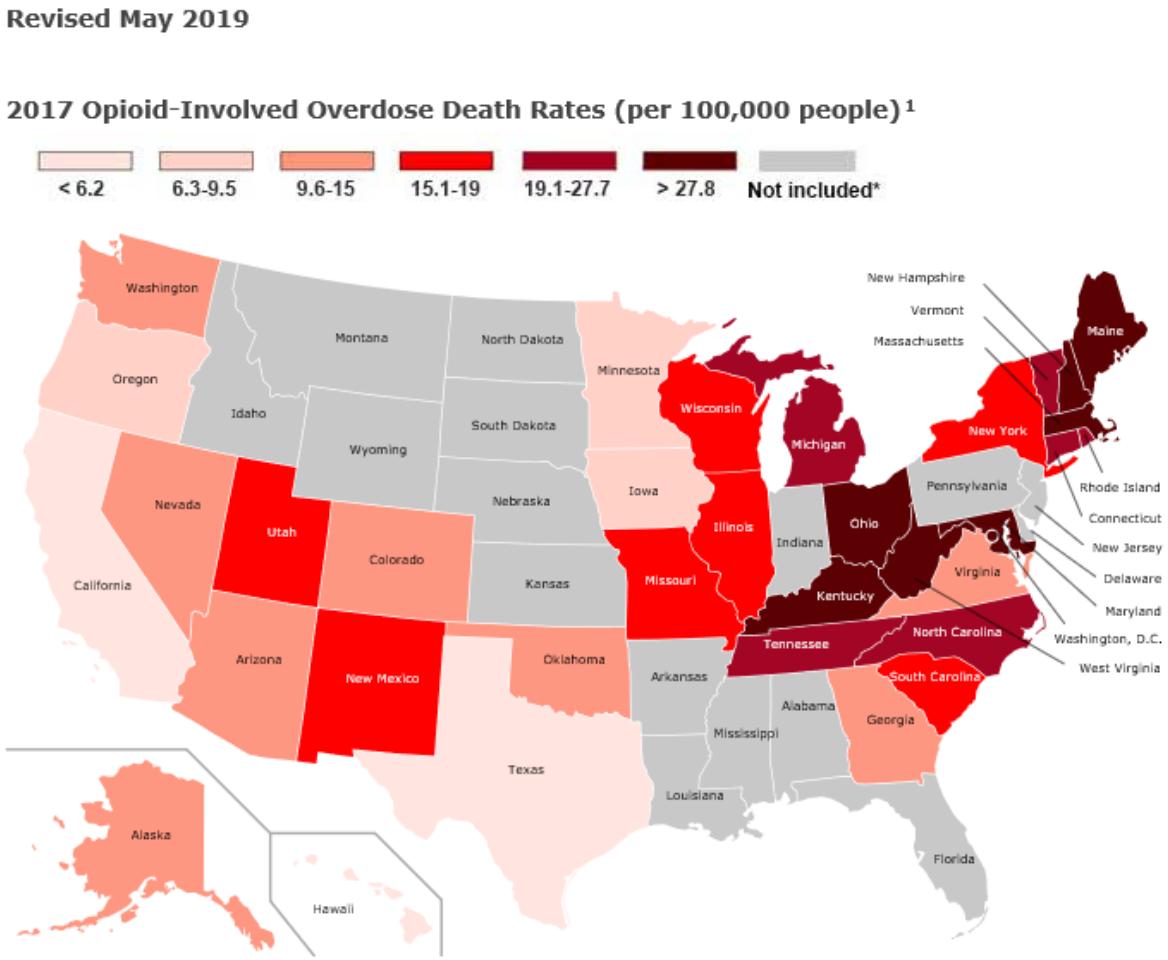
- Prescription Drug Monitoring Programs (state-level)
- Overdose deaths
- Criminal justice data
- Substance use disorder treatment
- Survey data
  - Existing surveys
  - Information collected prospectively (e.g., patient-reported outcomes/patient input)

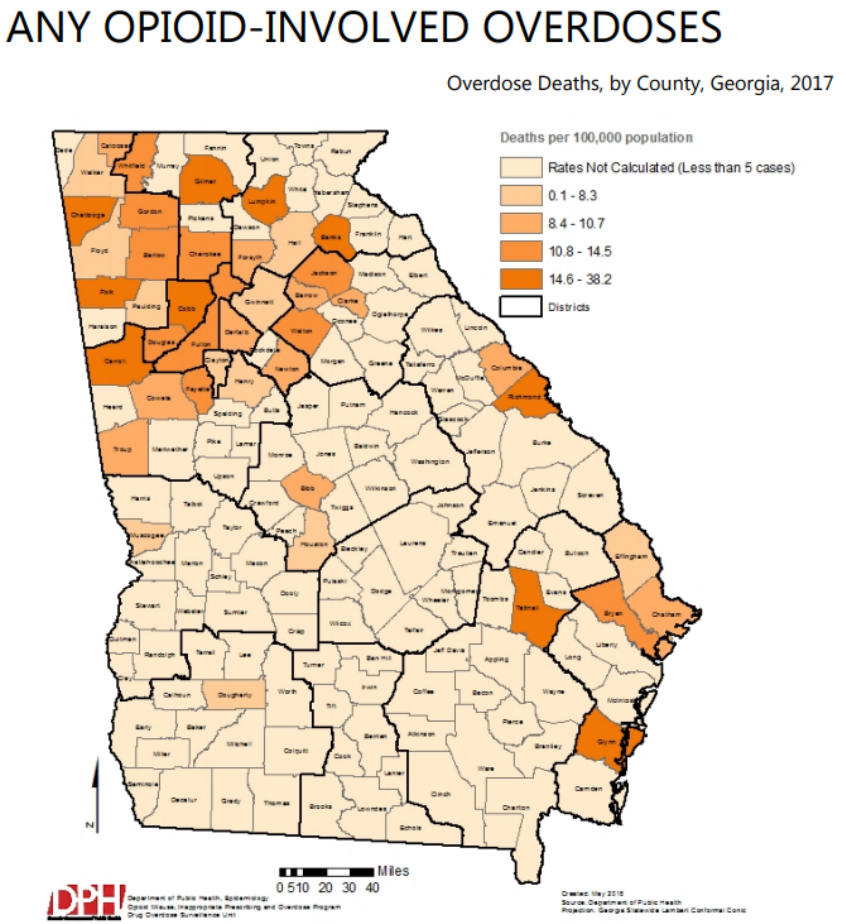
FDA is Funding Research to Enhance Linkages for Opioid Overdose Surveillance

- 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

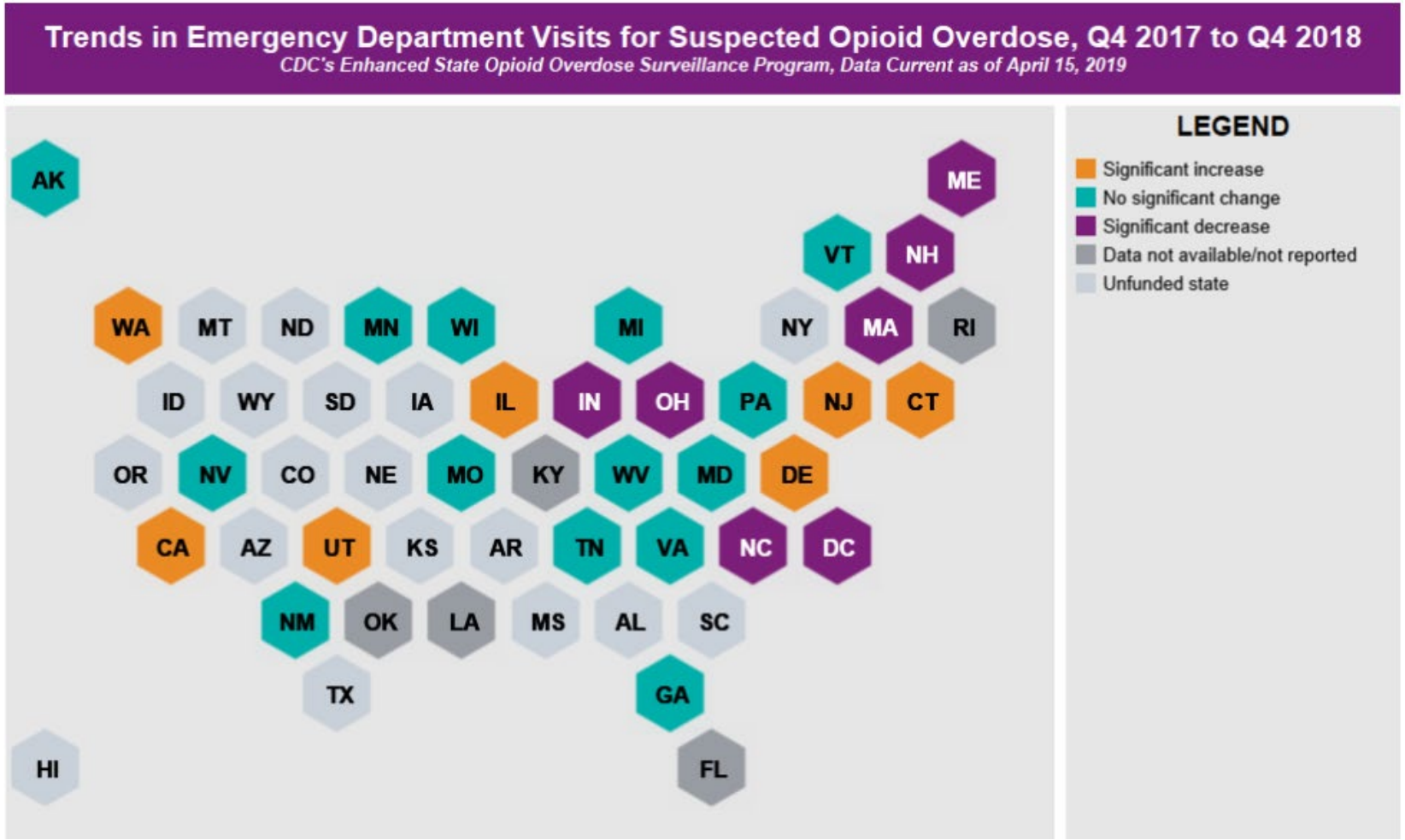




Source: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state

Source: https://dph.georgia.gov/sites/dph.georgia.gov/files/2017%20Preliminary%20Georgia%20Opioid%20Overdose%20Report.pdf

Time Trends



Source: https://www.cdc.gov/drugoverdose/data/nonfatal/nonfatal-opioids.html

Opioids and Benzodiazepines – National Estimates and Ecological Associations

41% relative increase in co-prescribing

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

Characteristic	2002[b]	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
All opioid recipients	6.8	6.6	6.8	7.3	7.6	8.2	8.6	8.5	8.5	8.6	8.7	8.5	9.6
Gender													
Male	5.5	5.2	5.4	5.8	6.1	6.7	7.0	6.9	7.0	7.0	7.0	6.8	7.7
Female	7.7	7.5	7.8	8.3	8.6	9.3	9.8	9.6	9.6	9.7	9.9	9.7	11.0
Age													
0–17 years	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.7
18–44 years	4.5	4.4	4.5	5.0	5.4	6.0	6.4	6.1	6.2	6.2	6.1	5.5	6.4
45–64 years	8.8	8.4	8.7	9.2	9.6	10.3	10.8	11.2	11.0	11.2	11.4	11.2	12.3
65+ years	11.1	10.5	10.6	10.7	9.9	10.3	10.6	11.0	11.0	11.2	11.3	11.2	12.0
Chronic users[c]	41.4	39.1	39.3	39.5	37.2	37.8	37.7	40.5	40.3	39.7	38.0	35.5	33.9
Non-chronic users[c]	3.6	3.5	3.5	3.6	3.7	4.1	4.3	4.1	4.2	4.3	4.4	4.4	5.4

Source: IMS Health Vector One®: Data Extract Tool, 2002–2014.
Note: Values are percentages.
[a]Patients were considered concomitant users if they had one or more opioid and benzodiazepine episodes that overlapped by 7 or more consecutive days.
[b]Percent of concomitant patients, out of the total number of opioid recipients during a given calendar year.
[c]Patients with at least one opioid episode ≥90 days during the study period were considered chronic opioid users. All other patients were considered non-chronic opioid users. For chronic opioid users, concomitancy proportions were based on opioid episodes ≥90 days only.

Hwang et al / Am J Prev Med 2016;51(2):151–160

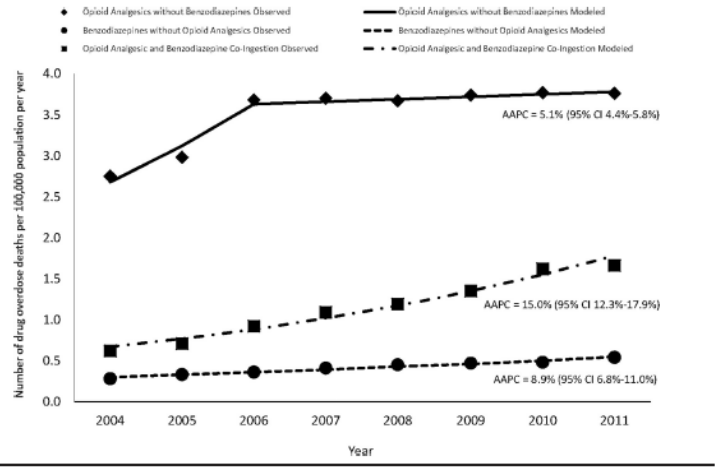
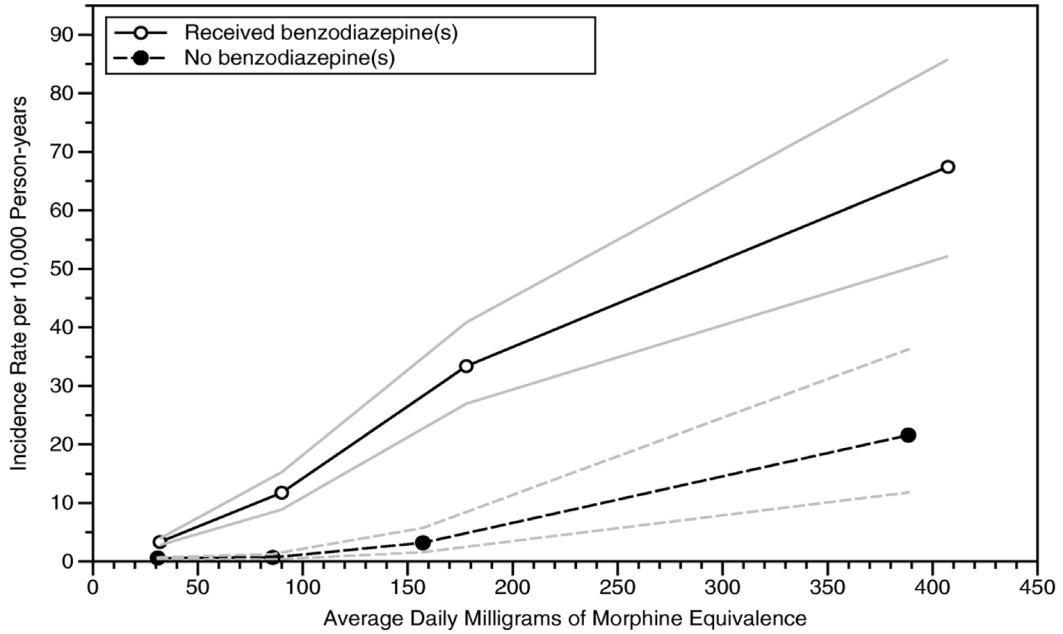


Figure 2. Trends in opioid analgesic and benzodiazepine drug overdose deaths, U.S., 2004–2011.

Source: Hwang et al, Am J Prev Med 2016;51(2):151-160 and Jones CM, Mcaninch JK, Am J Prev Med 2015;49(4):493-501.

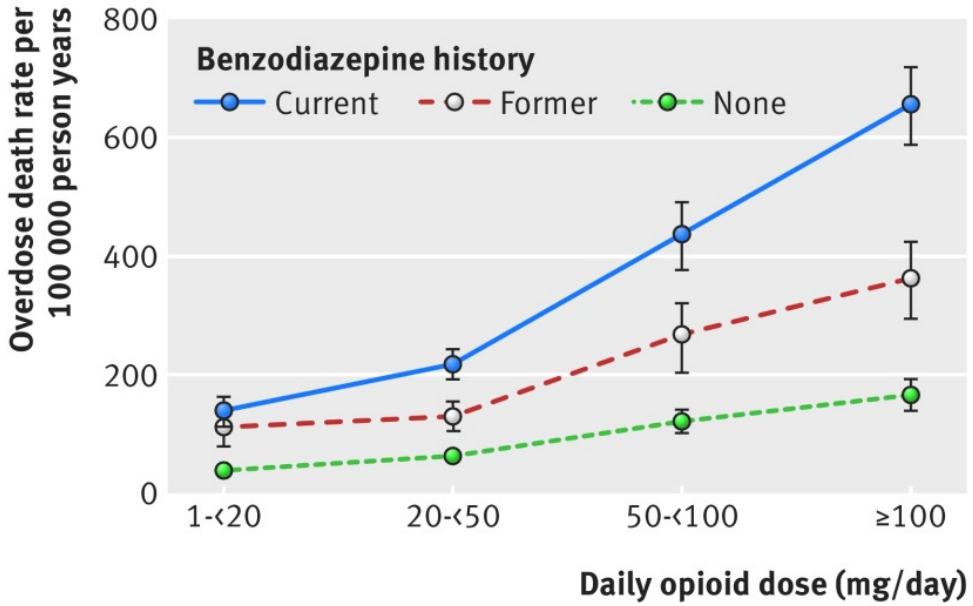
Opioids and Benzodiazepines – Local Data with Linkages

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.

Source: Dasgupta et al, Pain Medicine 2016;17:85-98 and Park et al, BMJ 2015;350:h2698

"4th Wave" of Opioid Overdose Crisis

Overdose deaths, US

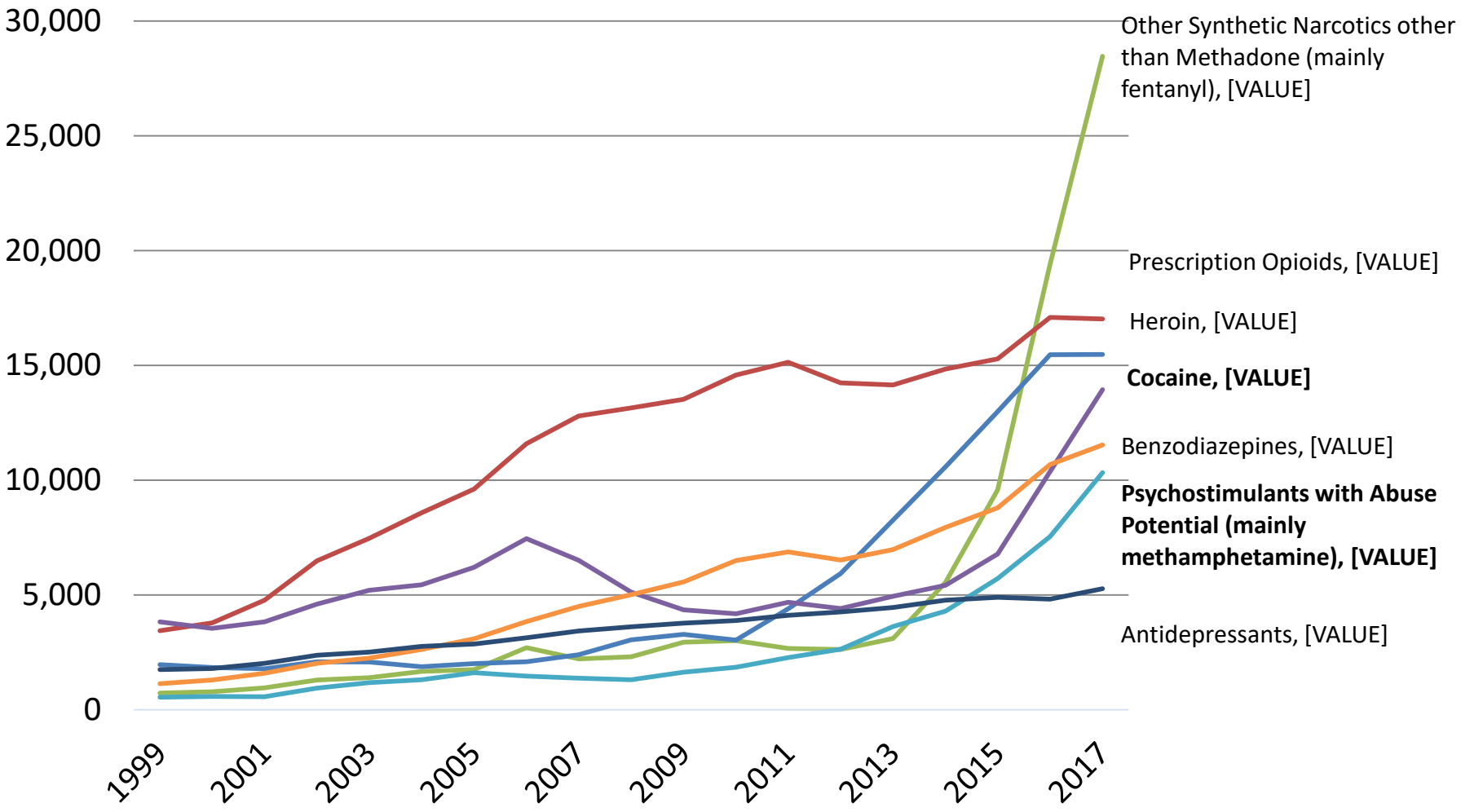
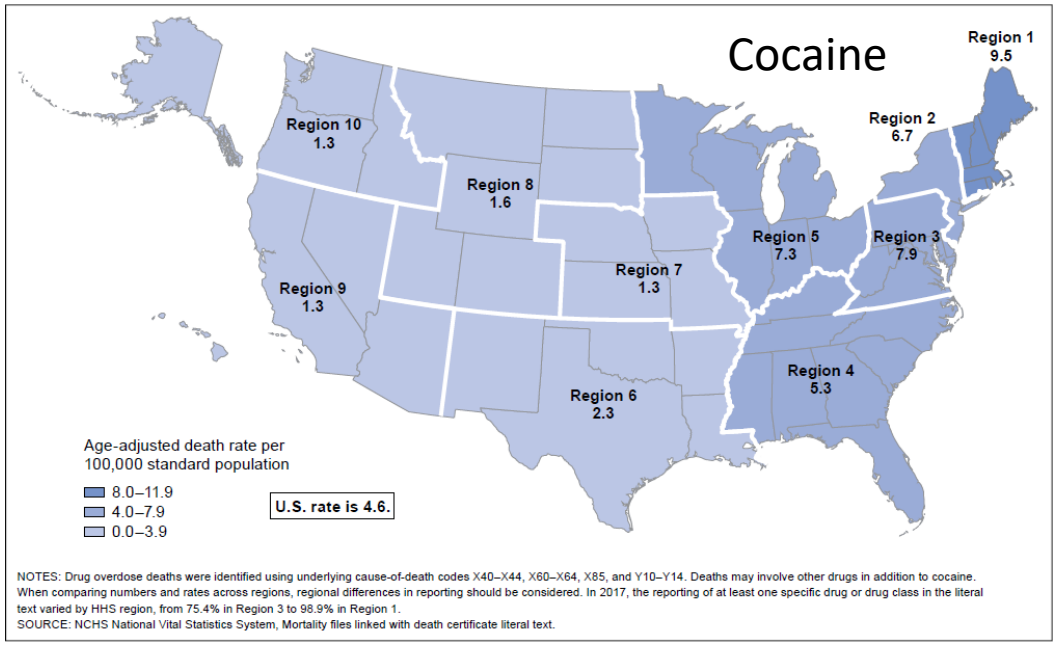
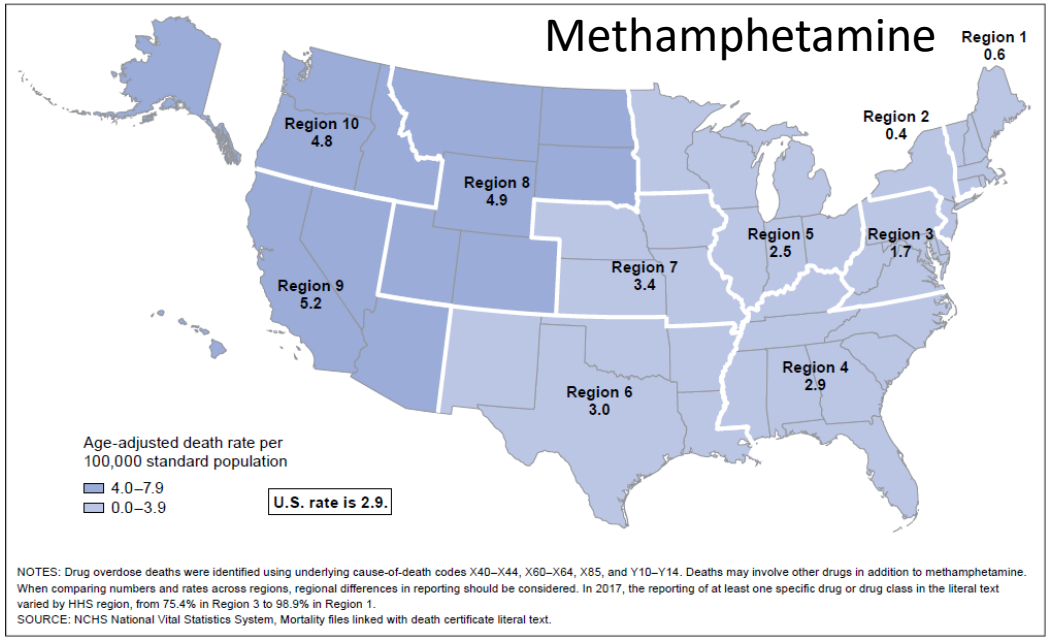


Figure Source: National Institute on Drug Abuse. **Data Source:** CDC Wonder.

Geographic Variation: Age-adjusted overdose death rates, 2017



NOTES: Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to cocaine. When comparing numbers and rates across regions, regional differences in reporting should be considered. In 2017, the reporting of at least one specific drug or drug class in the literal text varied by HHS region, from 75.4% in Region 3 to 98.9% in Region 1.
SOURCE: NCHS National Vital Statistics System, Mortality files linked with death certificate literal text.



NOTES: Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to methamphetamine. When comparing numbers and rates across regions, regional differences in reporting should be considered. In 2017, the reporting of at least one specific drug or drug class in the literal text varied by HHS region, from 75.4% in Region 3 to 98.9% in Region 1.
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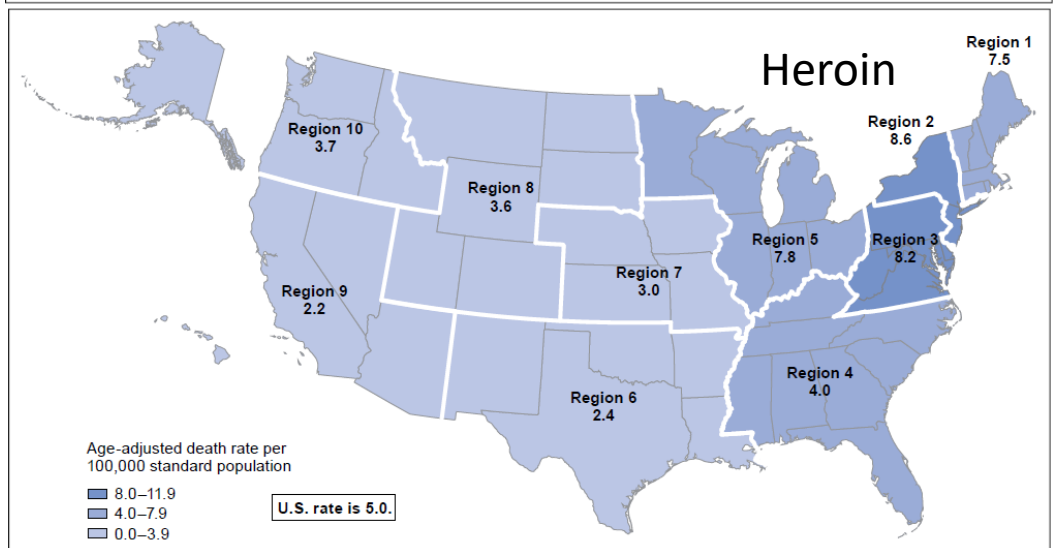

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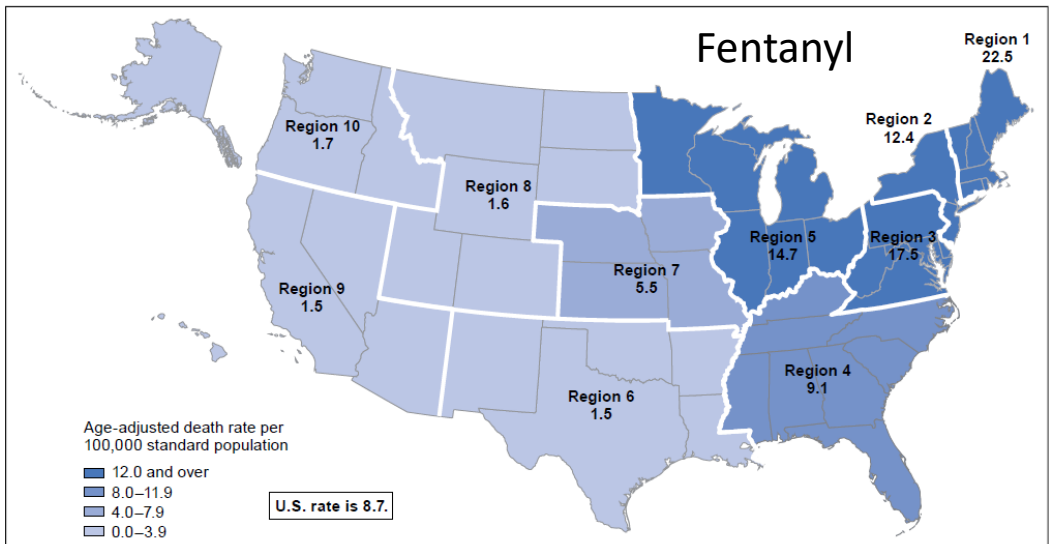
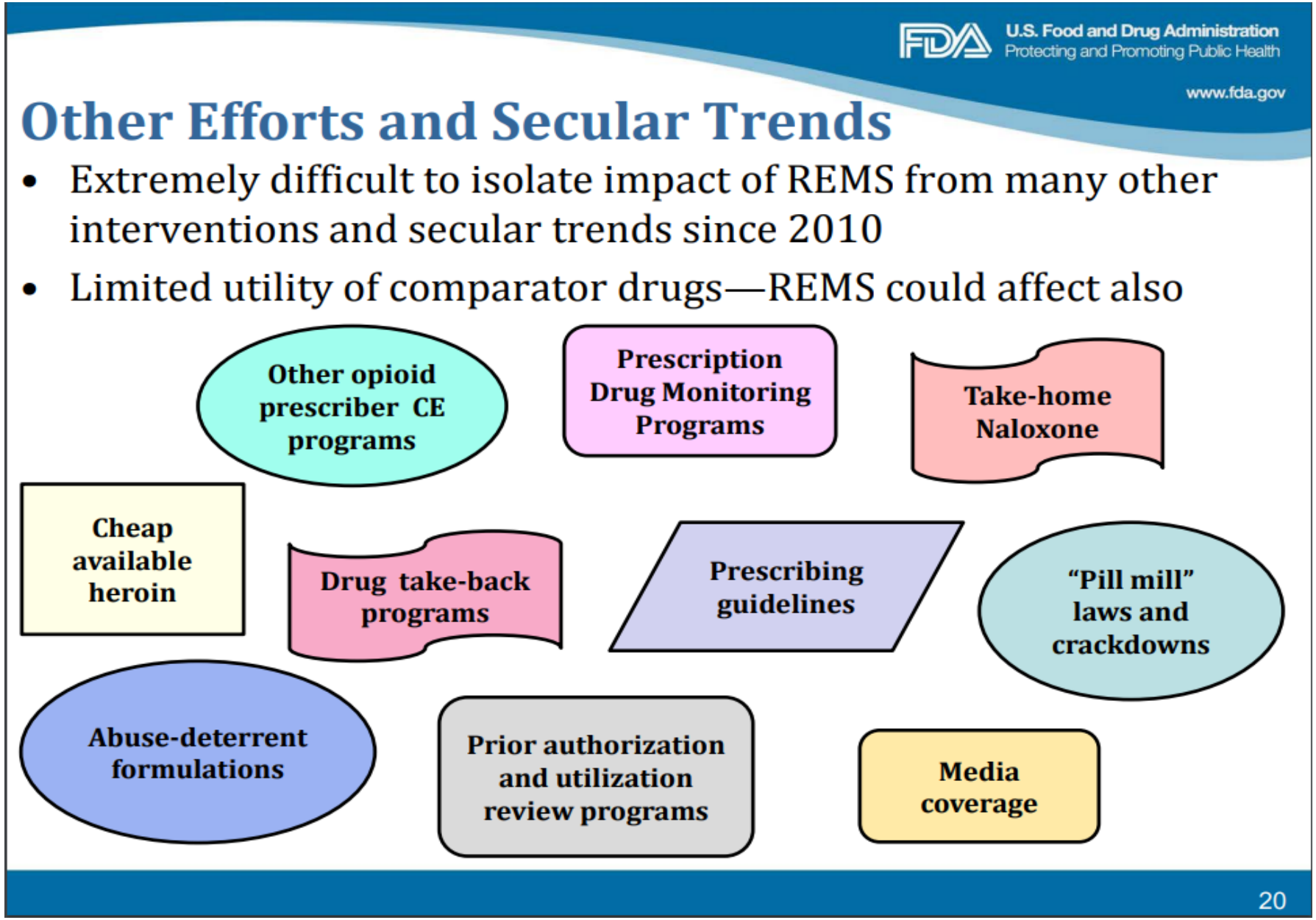


NOTES: Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to fentanyl. When comparing numbers and rates across regions, regional differences in reporting should be considered. In 2017, the reporting of at least one specific drug or drug class in the literal text varied by HHS region, from 75.4% in Region 3 to 98.9% in Region 1.
SOURCE: NCHS National Vital Statistics System, Mortality files linked with death certificate literal text.

Hedegaard H et al. Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. *National Vital Statistics Reports.* 2019;68(12):1.

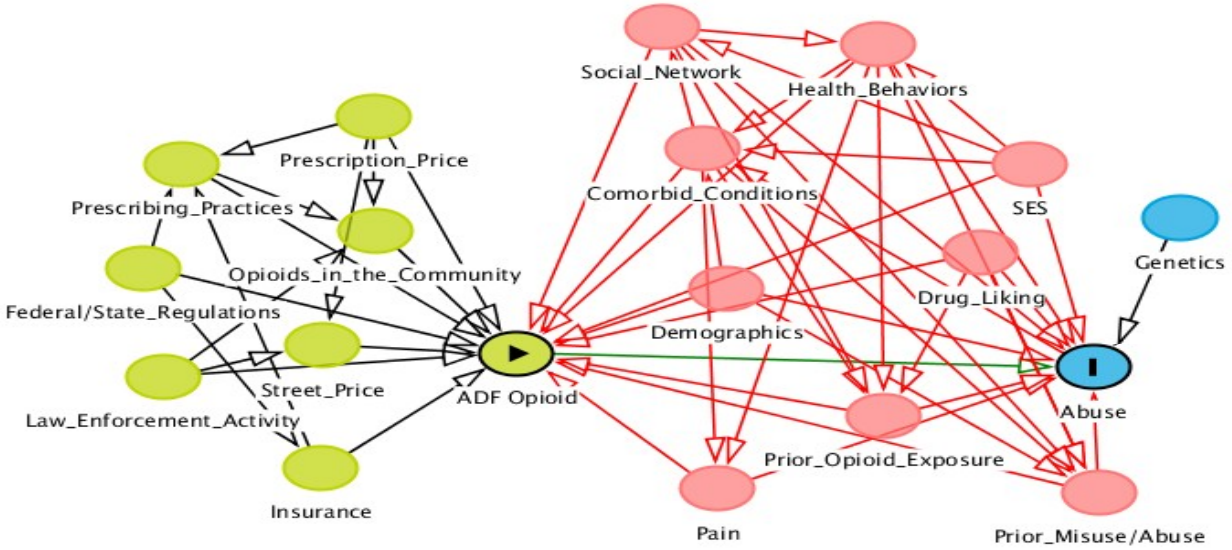
Confounders
(*comparative*)



Source: https://www.fda.gov/media/97531/download

This is What We Would Like

This is the Reality – Confounders



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

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?


FDA
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ADMINISTRATION