One Drug? Two Drugs?
Polydrug Mortality Is More Common Than We Think
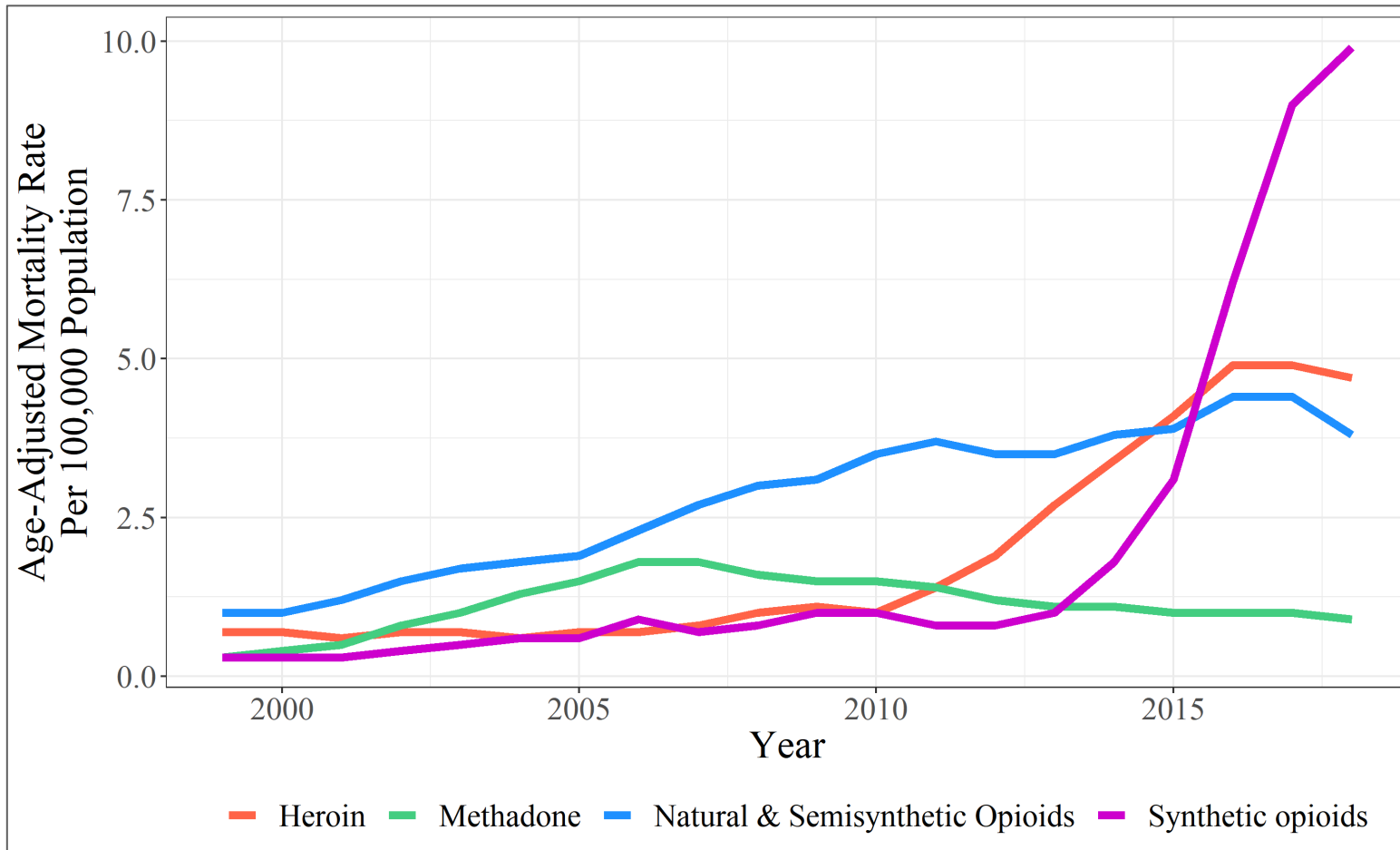
Joshua C. Black, Ph.D.

Rocky Mountain Poison & Drug Safety

Outline

- Background and Hypotheses

- Analytic Strategy

- Polydrug deaths over time

- Network map of drug mentions on overdose deaths

- Next steps after COVID-19

Background
Drug Overdose Deaths in the United States

Summary[1]:

- Drug overdose deaths fell from 2017 to 2018
- Heroin, methadone, and natural & synthetic opioids fell
- Synthetic opioids continued to rise

[1]Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2018. NCHS Data Brief, no 356. Hyattsville, MD: National Center for Health Statistics. 2020

Objectives
Quantifying Polydrug Overdose

- Seek to understand polydrug mortality from a multivariable perspective

- Assume:

  – Specific drug mentions on death certificates inform polydrug involvement

- Hypotheses:

  1. Single drug deaths are uncommon

  2. Polydrug deaths are rising

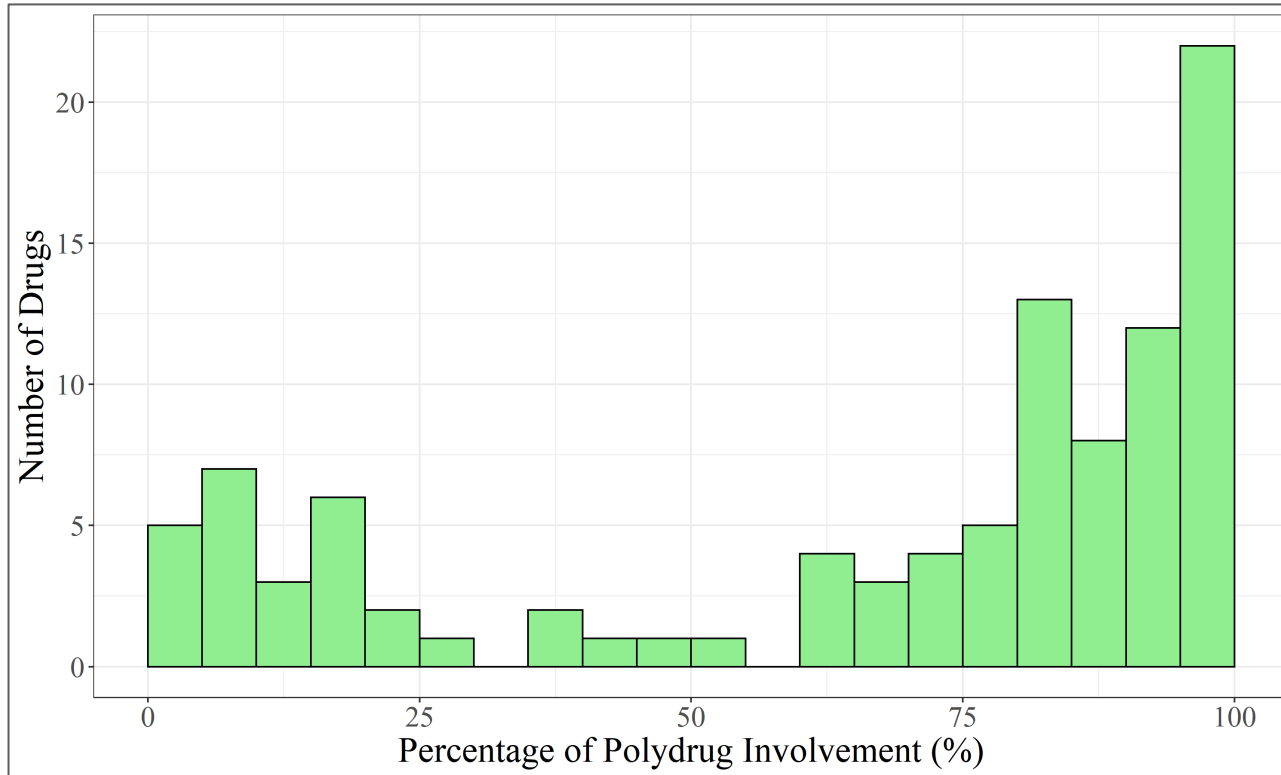 3. Drugs cluster into latent classes defining types of overdose deaths

Study Design

- Data Source: Drug Involved Mortality Database
  - List of drug-related terms in Part I, II, and Box 43 of death certificates
  - Used PubChem IDs to mark specific drug mentions
  - Further collapsed terms based on:
    - Metabolites: *α-HYDROXYALPRAZOLAM → ALPRAZOLAM*
    - Common terms: *BEER → ETHANOL*
- Setting: All decedents in the 50 states and DC; 2010-2017
- Statistical Analysis:
  - Percentage involving more than 1 specific drug
  - Network map analysis

Polydrug Mentions Over Time

Prevalence of Polydrug Mortality
Polydrug Involvement

Number of Drugs vs. Percentage of Polydrug Involvement (%)

Drug	Total Deaths	Polydrug (%)
Oxycodone	47,269	81.5
Alprazolam	39,234	97.3
Morphine	33,893	77.5
Methadone	32,924	68.2
Hydrocodone	27,104	85.6

- Among deaths mentioning a drug, percentage mentioning 2nd drug (or more)
- Top 100 drugs
- For 60 drugs, ≥75% of deaths were polydrug deaths

All specific drug mentions
2010-2017

Polydrug Mortality, 2010 to 2017

Change in Polydrug Percentage, 2010 to 2017 (Δ%)

Labels on chart:
- COCAINE: 23.5%
- BUPRENORPHINE: 18.5%
- TRAMADOL: 8.5%
- AMITRIPTYLINE: 7.2%
- CITALOPRAM: 5%
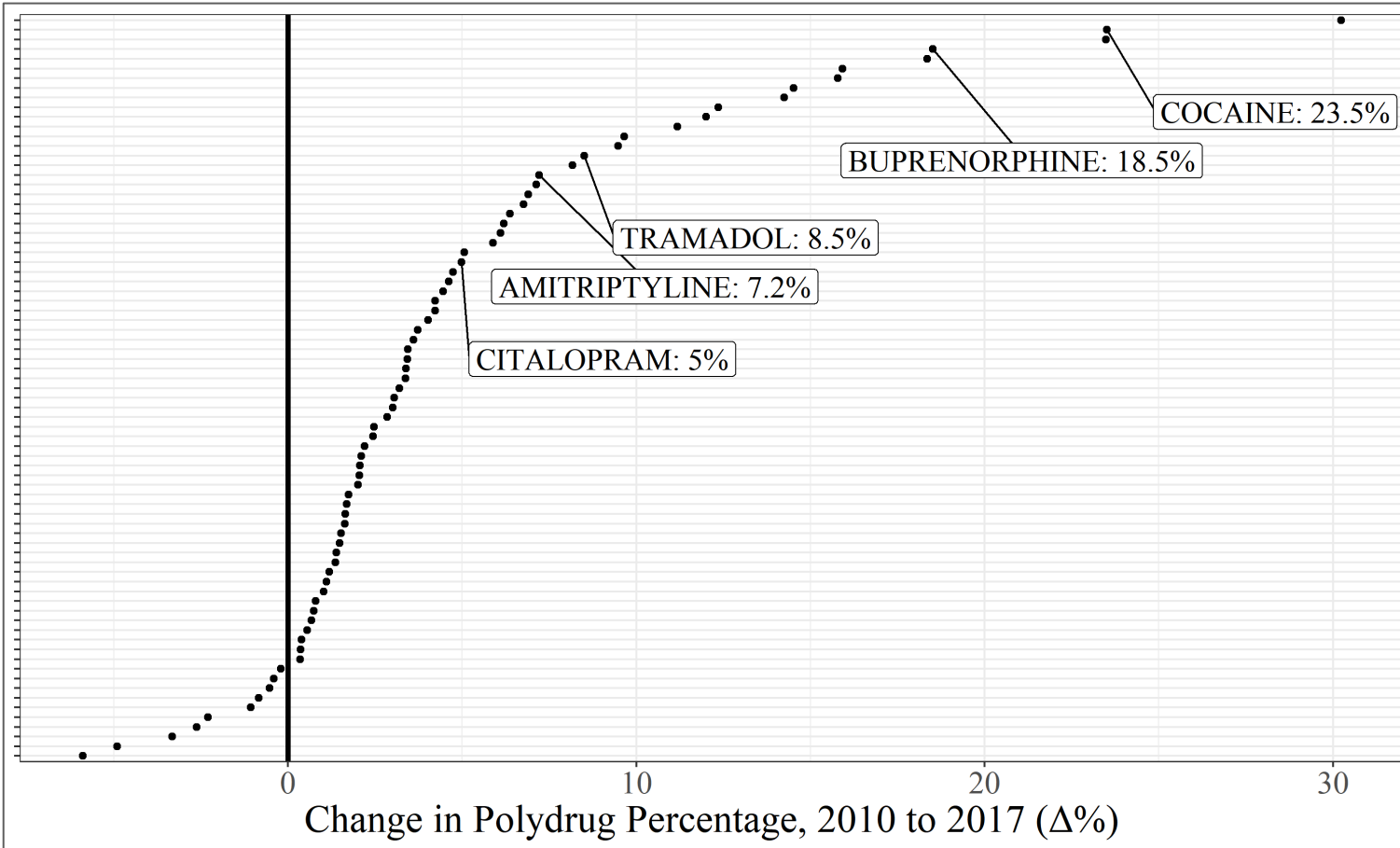
Drug (n)	Polydrug (%)	
	2010	2017
Cocaine (77,045)	50.2	73.7
Buprenorphine (3,360)	75.0	93.5
Tramadol (9,064)	77.9	86.4
Amitriptyline (6,803)	81.0	88.3
Citalopram (8,431)	90.4	95.4

- Most drugs in the Top 100 increased in percentage of polydrug involvement
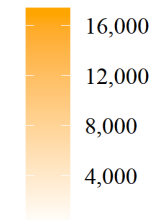
All specific drug mentions

Analysis of Pairwise Combinations

Fentanyl Deaths
Number with second substance
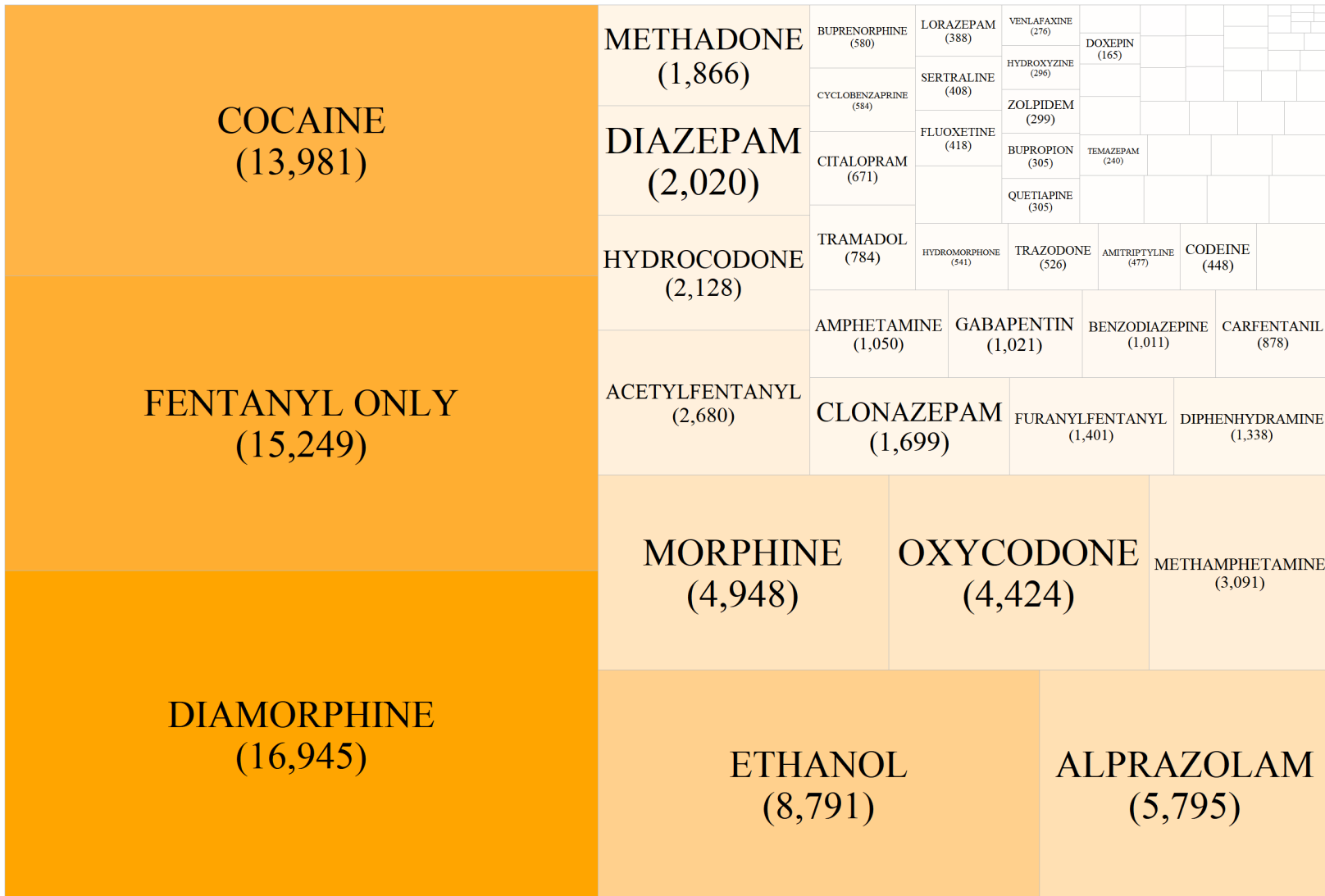
Total Fentanyl Deaths: 60,526
Fentanyl Only: 25.2%

Treemap categories:

- COCAINE (13,981)
- FENTANYL ONLY (15,249)
- DIAMORPHINE (16,945)
- METHADONE (1,866)
- DIAZEPAM (2,020)
- HYDROCODONE (2,128)
- ACETYLFENTANYL (2,680)
- MORPHINE (4,948)
- OXYCODONE (4,424)
- METHAMPHETAMINE (3,091)
- ETHANOL (8,791)
- ALPRAZOLAM (5,795)
- BUPRENORPHINE (580)
- LORAZEPAM (388)
- VENLAFAXINE (276)
- DOXEPIN (165)
- CYCLOBENZAPRINE (584)
- SERTRALINE (408)
- HYDROXYZINE (296)
- ZOLPIDEM (299)
- CITALOPRAM (671)
- FLUOXETINE (418)
- BUPROPION (305)
- TEMAZEPAM (240)
- QUETIAPINE (305)
- TRAMADOL (784)
- HYDROMORPHONE (541)
- TRAZODONE (526)
- AMITRIPTYLINE (477)
- CODEINE (448)
- AMPHETAMINE (1,050)
- GABAPENTIN (1,021)
- BENZODIAZEPINE (1,011)
- CARFENTANIL (878)
- CLONAZEPAM (1,699)
- FURANYLFENTANYL (1,401)
- DIPHENHYDRAMINE (1,338)

Polysubstance Deaths

16,000
12,000
8,000
4,000

RADARS SYSTEM 2020
14TH ANNUAL SCIENTIFIC MEETING

Alprazolam Deaths
Number with second substance
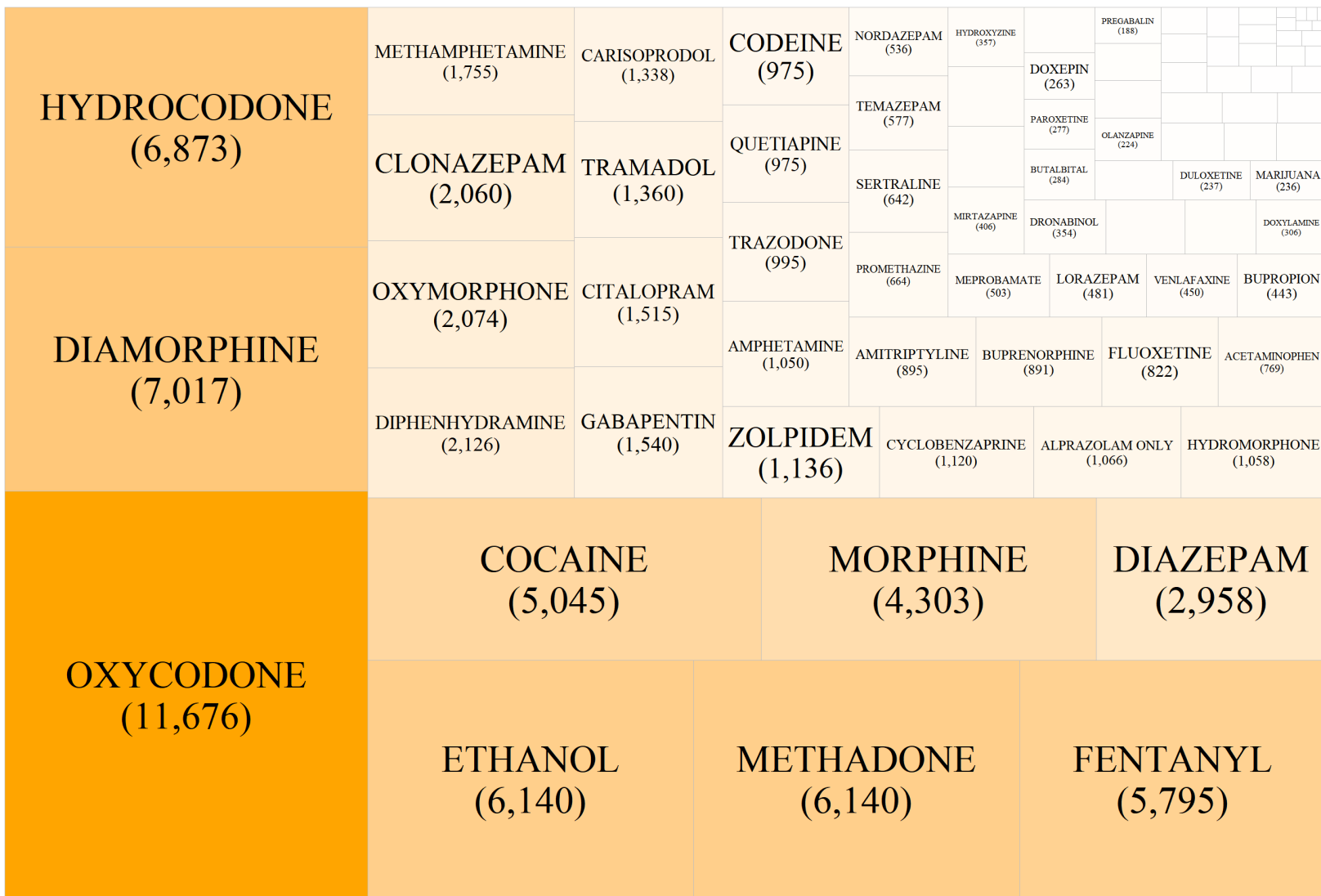
Total Alprazolam Deaths: 39,234
Alprazolam Only: 2.7%

Polysubstance Deaths

9,000
6,000
3,000

Substance	Count
HYDROCODONE	(6,873)
DIAMORPHINE	(7,017)
OXYCODONE	(11,676)
METHAMPHETAMINE	(1,755)
CARISOPRODOL	(1,338)
CODEINE	(975)
NORDAZEPAM	(536)
HYDROXYZINE	(357)
PREGABALIN	(188)
DOXEPIN	(263)
CLONAZEPAM	(2,060)
TRAMADOL	(1,360)
QUETIAPINE	(975)
TEMAZEPAM	(577)
PAROXETINE	(277)
OLANZAPINE	(224)
SERTRALINE	(642)
BUTALBITAL	(284)
DULOXETINE	(237)
MARIJUANA	(236)
OXYMORPHONE	(2,074)
CITALOPRAM	(1,515)
TRAZODONE	(995)
MIRTAZAPINE	(406)
DRONABINOL	(354)
DOXYLAMINE	(306)
PROMETHAZINE	(664)
MEPROBAMATE	(503)
LORAZEPAM	(481)
VENLAFAXINE	(450)
BUPROPION	(443)
AMPHETAMINE	(1,050)
AMITRIPTYLINE	(895)
BUPRENORPHINE	(891)
FLUOXETINE	(822)
ACETAMINOPHEN	(769)
DIPHENHYDRAMINE	(2,126)
GABAPENTIN	(1,540)
ZOLPIDEM	(1,136)
CYCLOBENZAPRINE	(1,120)
ALPRAZOLAM ONLY	(1,066)
HYDROMORPHONE	(1,058)
COCAINE	(5,045)
MORPHINE	(4,303)
DIAZEPAM	(2,958)
ETHANOL	(6,140)
METHADONE	(6,140)
FENTANYL	(5,795)

RADARS SYSTEM 2020
14TH ANNUAL SCIENTIFIC MEETING

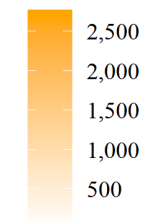# Diphenhydramine Deaths
Number with second substance
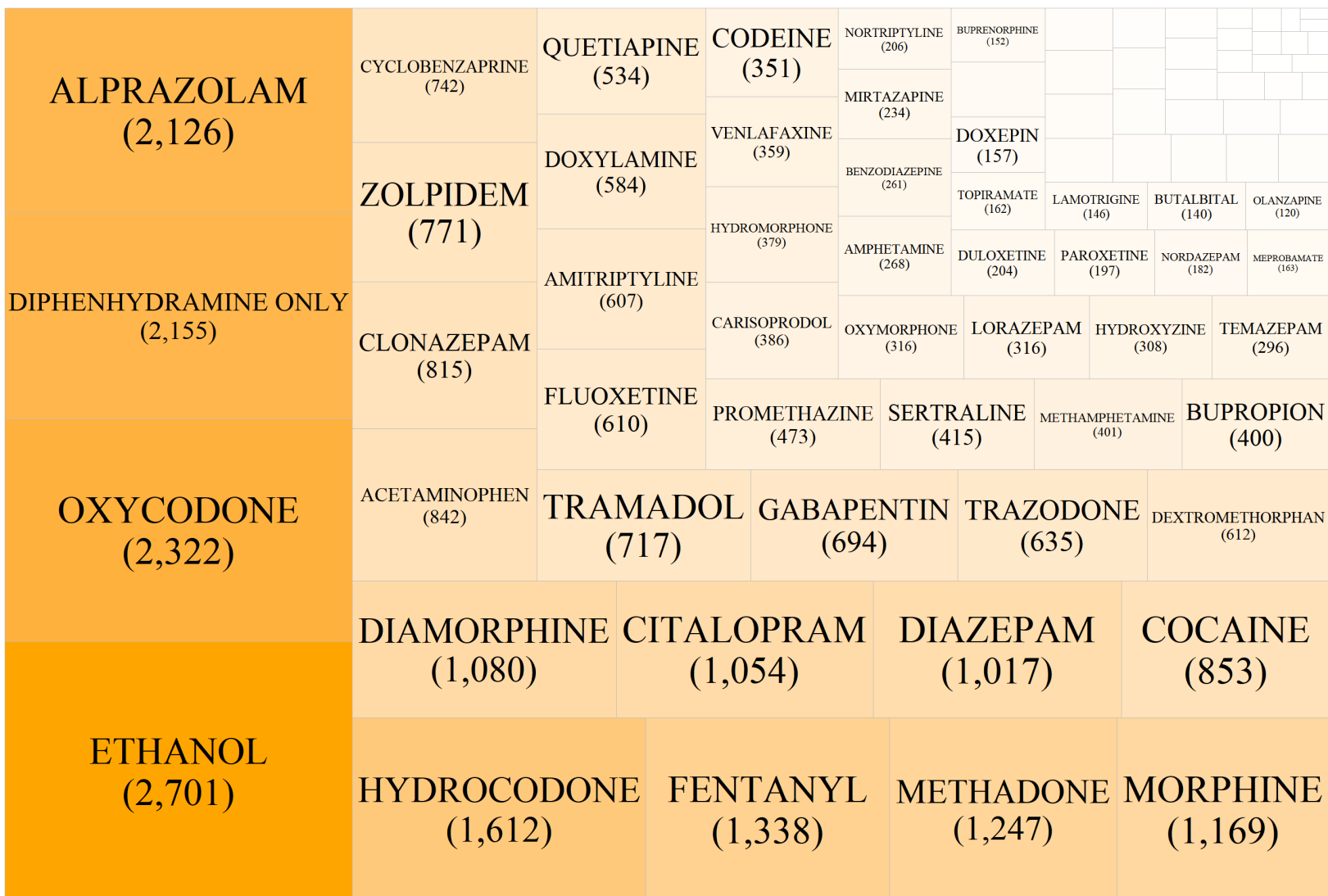
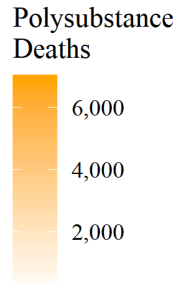Total Diphenhydramine Deaths: 13,886
Diphenhydramine Only: 15.5%

ALPRAZOLAM (2,126)

DIPHENHYDRAMINE ONLY (2,155)

OXYCODONE (2,322)

ETHANOL (2,701)

CYCLOBENZAPRINE (742)
ZOLPIDEM (771)
CLONAZEPAM (815)
ACETAMINOPHEN (842)

QUETIAPINE (534)
DOXYLAMINE (584)
AMITRIPTYLINE (607)
FLUOXETINE (610)

CODEINE (351)
VENLAFAXINE (359)
HYDROMORPHONE (379)
CARISOPRODOL (386)

NORTRIPTYLINE (206)
MIRTAZAPINE (234)
BENZODIAZEPINE (261)
AMPHETAMINE (268)

BUPRENORPHINE (152)
DOXEPIN (157)
TOPIRAMATE (162)
LAMOTRIGINE (146)
BUTALBITAL (140)
OLANZAPINE (120)
DULOXETINE (204)
PAROXETINE (197)
NORDAZEPAM (182)
MEPROBAMATE (163)

OXYMORPHONE (316)
LORAZEPAM (316)
HYDROXYZINE (308)
TEMAZEPAM (296)

PROMETHAZINE (473)
SERTRALINE (415)
METHAMPHETAMINE (401)
BUPROPION (400)

TRAMADOL (717)
GABAPENTIN (694)
TRAZODONE (635)
DEXTROMETHORPHAN (612)

DIAMORPHINE (1,080)
CITALOPRAM (1,054)
DIAZEPAM (1,017)
COCAINE (853)

HYDROCODONE (1,612)
FENTANYL (1,338)
METHADONE (1,247)
MORPHINE (1,169)

Polysubstance Deaths

2,500
2,000
1,500
1,000
500

RADARS SYSTEM 2020
14TH ANNUAL SCIENTIFIC MEETING

Hydrocodone Deaths
Number with second substance

Total Hydrocodone Deaths: 27,104

Hydrocodone Only: 14.4%

Polysubstance Deaths
6,000
4,000
2,000

OXYCODONE (4,460)

ETHANOL (4,732)

ALPRAZOLAM (6,873)

CARISOPRODOL (1,500)

CLONAZEPAM (1,527)

DIPHENHYDRAMINE (1,612)

DIAMORPHINE (1,680)

OXYMORPHONE (845)

METHAMPHETAMINE (1,034)

ZOLPIDEM (1,096)

HYDROMORPHONE (1,112)

CYCLOBENZAPRINE (1,192)

TEMAZEPAM (532)

PROMETHAZINE (575)

DIHYDROCODEINE (593)

FLUOXETINE (604)

AMITRIPTYLINE (829)

GABAPENTIN (1,141)

CITALOPRAM (1,139)

TRAMADOL (1,137)

BUPROPION (320)

VENLAFAXINE (381)

NORDAZEPAM (408)

SERTRALINE (430)

LORAZEPAM (492)

AMPHETAMINE (491)

BENZODIAZEPINE (478)

MEPROBAMATE (461)

TRAZODONE (764)

CODEINE (721)

QUETIAPINE (689)

PAROXETINE (200)

OLANZAPINE (123)

PREGABALIN (132)

TOPIRAMATE (153)

NORTRIPTYLINE (223)

HYDROXYZINE (234)

DULOXETINE (199)

DRONABINOL (198)

DOXEPIN (181)

OXAZEPAM (122)

MIRTAZAPINE (282)

DOXYLAMINE (248)

BUTALBITAL (238)

FENTANYL (2,128)

METHADONE (1,942)

ACETAMINOPHEN (1,938)

COCAINE (1,710)

HYDROCODONE ONLY (3,909)

DIAZEPAM (2,724)

MORPHINE (2,603)

Overdose Network Map
Pairwise Mentions (Top 25)

- Thicker lines represent higher number of deaths involving both drugs
- More central points represent larger number of strong connections
- Four major drugs: fentanyl, cocaine, heroin, ethanol
- Central drugs in combination more often
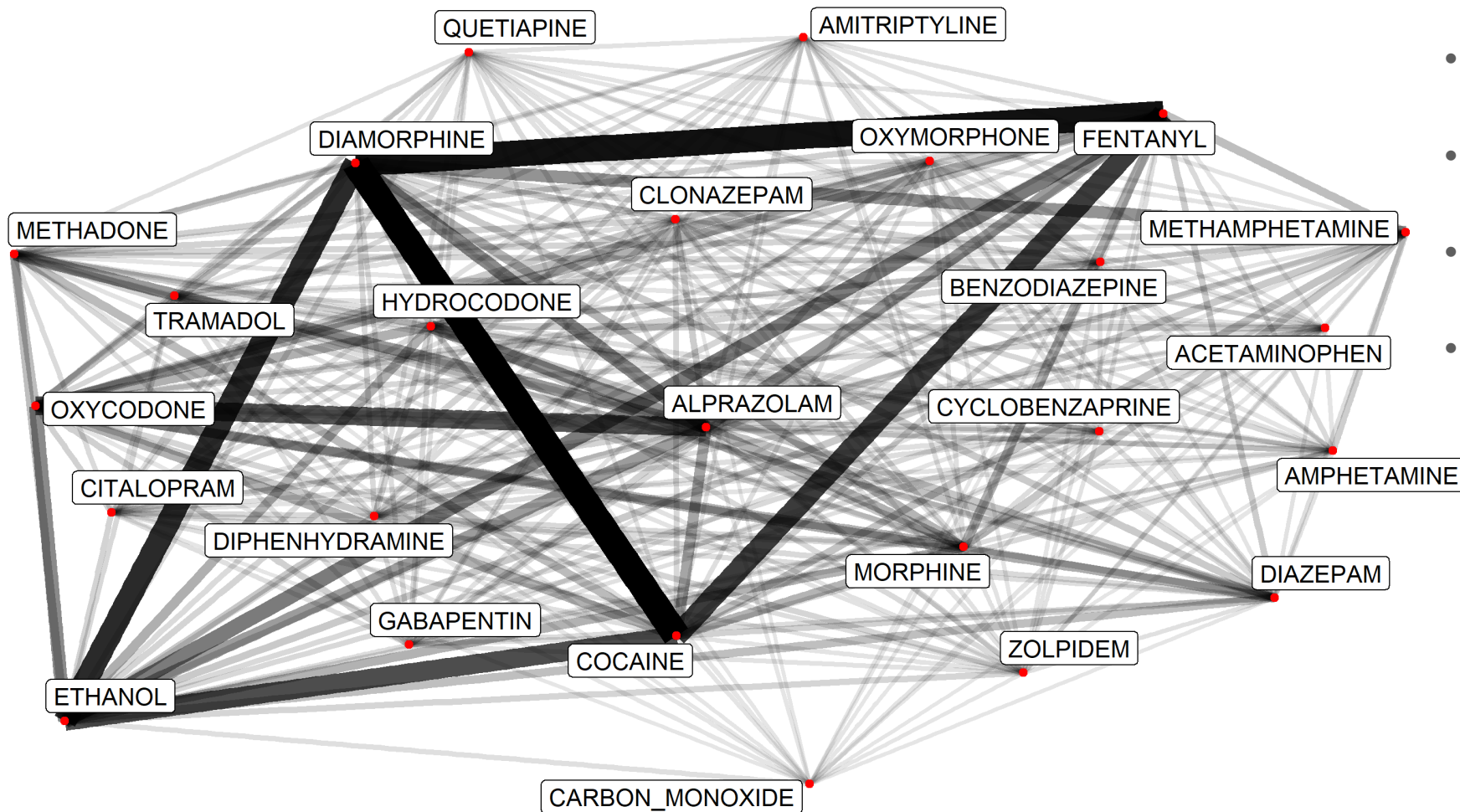
Polysubstance Deaths —— 4,000 ▬ 8,000 ▬ 12,000 ▬ 16,000

Next Steps and Conclusions

Post-COVID Steps

- Analysis halted due to pandemic closures

- Analyze combinations of 3 and greater

- Formally quantify network map into clusters

  – Multiple Correspondence Analysis (high dimensional method)

- Subgroup networks (e.g., opioids, stimulants)

Conclusions

- Diverse drug combinations and interactions lead to death

  – Attributing mortality to a single drug does not provide a full picture of drug risk

- Single-substance deaths are a minority for many prescription drugs in the top 100 substances

- Limitations

  – Death certificates not complete list of drugs involved

  – Class terms that are also specific drugs were counted as specific drugs (e.g., "BENZODIAZEPINE")

  – Practices for entering data on death certificates shifts over time

Questions?

Joshua C. Black, Ph.D.

Joshua.black@rmpds.org