One Drug? Two Drugs?
Polydrug Mortality Is More Common Than We Think

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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
Summary:

- Drug overdose deaths fell from 2017 to 2018
- Heroin, methadone, and natural & synthetic opioids fell
- Synthetic opioids continued to rise
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: \( \alpha\text{-HYDROXYALPRAZOLAM} \rightarrow \text{ALPRAZOLAM} \)
    • Common terms: \( \text{BEER} \rightarrow \text{ETHANOL} \)

• 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

- Among deaths mentioning a drug, percentage mentioning 2\textsuperscript{nd} drug (or more)
- Top 100 drugs
- For 60 drugs, \(\geq75\%\) of deaths were polydrug deaths

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Deaths</th>
<th>Polydrug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>47,269</td>
<td>81.5</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>39,234</td>
<td>97.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>33,893</td>
<td>77.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>32,924</td>
<td>68.2</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>27,104</td>
<td>85.6</td>
</tr>
</tbody>
</table>

All specific drug mentions 2010-2017
Polydrug Mortality, 2010 to 2017

<table>
<thead>
<tr>
<th>Drug (n)</th>
<th>Polydrug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
</tr>
<tr>
<td>Cocaine (77,045)</td>
<td>50.2</td>
</tr>
<tr>
<td>Buprenorphine (3,360)</td>
<td>75.0</td>
</tr>
<tr>
<td>Tramadol (9,064)</td>
<td>77.9</td>
</tr>
<tr>
<td>Amitriptyline (6,803)</td>
<td>81.0</td>
</tr>
<tr>
<td>Citalopram (8,431)</td>
<td>90.4</td>
</tr>
</tbody>
</table>

- 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%
Alprazolam Deaths
Number with second substance

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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPRAZOLAM</td>
<td>(2,126)</td>
</tr>
<tr>
<td>ZOLPIDEM</td>
<td>(771)</td>
</tr>
<tr>
<td>DIPHENDRHYDRAMINE ONLY</td>
<td>(2,155)</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>(2,322)</td>
</tr>
<tr>
<td>ETHANOL</td>
<td>(2,701)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone only (%)</td>
<td>14.4%</td>
</tr>
</tbody>
</table>

### Total Hydrocodone Deaths: 27,104
Hydrocodone Only: 14.4%

### Polysubstance Deaths
- 6,000
- 4,000
- 2,000
• 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
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?

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