Thinking Outside the Opioid Box: Non-Opioid Pharmaceutical Abuse

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Roadmap

• Why nonopioid prescription drug misuse and abuse is increasingly common

• Framework for identifying nonopioid drug misuse and abuse

• Highlights of drug classes

• Gaps in knowledge
Why is nonopioid prescription drug misuse and abuse increasingly common?
Non-Opioid Prescription Drugs

- Potentiate effects of opioids
- “Smooth out” effects of other drugs
- Used as substitution or replacement when drug of choice not available
Framework for Identifying Non-Opioid Drug Misuse and Abuse
Surveillance Data

• National Poison Data System (NPDS)
## NPDS Intentional Abuse Rates

<table>
<thead>
<tr>
<th>Generic Code</th>
<th>Intentional Abuse</th>
<th>Single Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>51275</td>
<td>15895</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>18182</td>
<td>12852</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>13833</td>
<td>7402</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>8633</td>
<td>3375</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>8556</td>
<td>2982</td>
</tr>
<tr>
<td>Other Sedative/Hypnotic/Anti-Anxiety or Anti-Psychotic</td>
<td>8150</td>
<td>3700</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>5927</td>
<td>3163</td>
</tr>
<tr>
<td>Other SSRI</td>
<td>5185</td>
<td>1329</td>
</tr>
<tr>
<td>Other Antihistamines</td>
<td>5155</td>
<td>2208</td>
</tr>
<tr>
<td>Other Anticonvulsant (Excluding Barbiturates)</td>
<td>3931</td>
<td>1371</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>3662</td>
<td>2116</td>
</tr>
<tr>
<td>Other Antidepressant</td>
<td>3173</td>
<td>1133</td>
</tr>
<tr>
<td>Trazodone</td>
<td>3124</td>
<td>868</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>3017</td>
<td>1057</td>
</tr>
<tr>
<td>Other Muscle Relaxant</td>
<td>2989</td>
<td>1257</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>2948</td>
<td>853</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1373</td>
<td>379</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>1288</td>
<td>642</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1271</td>
<td>365</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1159</td>
<td>389</td>
</tr>
</tbody>
</table>
• Approaches to interpreting the data
  • Signal detection
    » Increased mentions
    » Increased single substance cases
    » Shift from intentional to unintentional
    » Increased cases in teenagers/young adults
Surveillance Data

- National Poison Data System (NPDS)
- General population surveys
  - Survey of Nonmedical Use of Prescription Drugs (NMURx)
Lifetime Use and Nonmedical Use

References: 9
Lifetime Nonmedical Use

Prevalence (95% CI)

- Cannabis
- Loperamide
- Heroin
- Benzodiazepines
- Non-pharmaceutical fentanyl
- Gaba-Analogues
Surveillance Data

• High risk groups
  – Department of Corrections, jails
  – Teenagers and young adults
  – Substance abuse treatment programs
  – Diversion
Highlights of Commonly Abused Non-Opioid Pharmaceuticals
GABA Analogs (Gabapentinoids)

- Gabapentin, pregabalin
- 10-15% prescribed opioids also prescribed gabapentin
- Misuse common in opioid use disorders (15-28%)
- Increased mortality when combined with opioids
  - Likely synergistic respiratory depression

References: 9 pt.
Gabapentin – NPDS 2011-2017

- Increased ratio of mentions to single exposure calls
  - Polysubstance cases on the rise
- Slight increase in proportion of intentional exposures
- Increased use in teenAGERS
Diversion of GABA Analogs

References: 9 pt.
Gabapentin and Mortality

<table>
<thead>
<tr>
<th></th>
<th>No. Exposed Cases</th>
<th>No. Exposed Controls</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Analysis</strong>: Recent Gabapentin Use</td>
<td>155 (12.3%)</td>
<td>313 (6.8%)</td>
<td>1.99 (1.61 to 2.47)</td>
<td>1.49 (1.18 to 1.88)</td>
</tr>
<tr>
<td><strong>Sensitivity Analysis</strong>: Overlapping Gabapentin Use*</td>
<td>121 (9.6%)</td>
<td>240 (5.2%)</td>
<td>1.98 (1.56 to 2.50)</td>
<td>1.46 (1.12 to 1.89)</td>
</tr>
<tr>
<td><strong>Secondary Analysis</strong>: Gabapentin Dose**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Dose</td>
<td>57 (4.5%)</td>
<td>101 (2.2%)</td>
<td>2.20 (1.58 to 3.08)</td>
<td>1.58 (1.09 to 2.27)</td>
</tr>
<tr>
<td>Moderate Dose</td>
<td>57 (4.5%)</td>
<td>111 (2.4%)</td>
<td>2.05 (1.46 to 2.87)</td>
<td>1.56 (1.06 to 2.28)</td>
</tr>
<tr>
<td>Low Dose</td>
<td>41 (3.3%)</td>
<td>101 (2.2%)</td>
<td>1.70 (1.17 to 2.48)</td>
<td>1.32 (0.89 to 1.97)</td>
</tr>
<tr>
<td><strong>Neutral Exposure†</strong>: Recent NSAID Use</td>
<td>480 (38.2%)</td>
<td>1647 (35.7%)</td>
<td>1.11 (0.98 to 1.27)</td>
<td>1.14 (0.98 to 1.32)</td>
</tr>
</tbody>
</table>

*1,256 cases and 4,619 controls; Reference Group: no gabapentin use
**Low dose: <900mg/day; moderate dose: 900-1799mg/day; high dose: ≥1800mg/day; Reference Group: no gabapentin use
†Reference Group: no NSAID use
††Reference Group: no NSAID use

Loperamide

- Antidiarrheal
- Prescription and OTC
- Intestinal mu agonist
- Poor systemic absorption due to p-glycoprotein
  - BUT often co-used with inhibitors
- Abused alone or in combination with opioids

References: 9 pt.
Loperamide – NPDS 2010-2017

• Ratio of mentions to single substance cases unchanged

• Increased proportion of intentional abuse cases
  • 8% -> 34%

• No significant change in rate of exposures, but behavior and reasons are changing
Loperamide Abuse

Miller H et al. JAPHA 2017, 57(2): S45–S50
## Reported Toxicities by Organ System

<table>
<thead>
<tr>
<th>Organ System</th>
<th>1985-2013 (n = 21)</th>
<th>2014-2016 (n = 33)</th>
<th>Total, 1985-2016 (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Neurological</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>17</td>
<td>27</td>
</tr>
</tbody>
</table>

Miller H et al. JAPHA 2017, 57(2): S45–S50
Antidepressants

- Reports of abuse of all classes
- May have higher rates with SNRI
  - Stimulant effects due to norepinephrine reuptake inhibition
  - When used with opioids, pharmaceutical “speedball” effect
- Adverse effects include seizures and dysrhythmias
Bupropion – NPDS 2012-2017

- Increased single substance exposures compared to total mentions
  - Used as a primary drug
- Increased proportion of intentional exposures
- Markedly increased use in teenage population

References: 9 pt.
Benzodiazepines

- GABA-A agonists
- Single agent and polysubstance exposures
- CNS depression
  - Can be synergistic with EtOH and opioids
- Respiratory depression rare with isolated oral exposure BUT also synergistic
### Table 2. Odds of death among people who were exposed to opioid analgesics compared to people who were exposed to benzodiazepines and/or opioid analgesics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Deaths/exposures (% resulting in death)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug of misuse or abuse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines + opioid analgesics</td>
<td>28/5342 (0.52%)</td>
<td>1.53 (1.00–2.34)</td>
<td>1.55 (1.01–2.37)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3/35,665 (0.01%)</td>
<td>0.02 (0.01–0.08)</td>
<td>0.03 (0.01–0.08)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>93/27,125 (0.34%)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85/36,210 (0.23%)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>39/31,922 (0.12%)</td>
<td>0.52 (0.36–0.76)</td>
<td>0.51 (0.35–0.74)</td>
</tr>
<tr>
<td><strong>Age (in increasing ten years increments)</strong></td>
<td>N/A</td>
<td>1.05 (0.93–1.18)</td>
<td>1.08 (0.96–1.21)</td>
</tr>
</tbody>
</table>

Calcaterra S et al, https://doi.org/10.1080/15563650.2018.1457792
Stimulants

- Used as single substance or polysubstance
  - Pharmaceutical "speedball" effect
- Highest rates in teenage and young adult population
- Rates of intentional abuse stable, but diversion increasing
Stimulants, Poison Centers

References: RADARS PC 3Q2017, intentional abuse cases
Stimulants, Drug Diversion

References: 9 pt.
Antipsychotics

• Atypical antipsychotics commonly abused both alone and in combination with other drugs
• Especially popular in incarcerated population
• Quetiapine often drug of choice
Antipsychotic Abuse

- 429 patients from detox and rehab units
- 73 (17%) abuse atypical antipsychotics with other substances
  - Alcohol, opioids, cocaine/crack, methamphetamine, cannabis
Antipsychotic Abuse

• Quetiapine most common (84.9%)
  • Olanzapine (17.8%), risperidone (24.7%), aripiprazole (20.5%), ziprasidone (8.1%), asenapine (2.9%)

• Goals: "getting mellow", "slowing down", or enhancing effects of other drugs
Quetiapine DAWN ED Visits

Cyclobenzaprine

- Reported via NPDS
- Few studies of misuse/abuse
- Anticholinergic effects
- Structural similarity to tricyclic antidepressants
- Anticipate synergistic CNS and respiratory depression with opioids
Other Antiepileptics

• Nearly all have been reported both in single substance and polysubstance abuse cases
• Levitiracetam may be on the horizon
• Synergistic CNS depression with opioids
• Cardiac effects also possible
Gaps in Knowledge

• What interventions are needed to decrease polysubstance abuse?
• Is postmarketing surveillance needed for nonopioid drugs?
• What education should be given to prescribers regarding risks?
Summary

- Nonopioid pharmaceutical drug abuse is becoming more common
- Many likely to be co-abused with opioids
- Synergistic CNS and respiratory depression most common interaction
- Need methods for surveillance and early warning
  - NPDS and NMURx may provide ideas
Questions?

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