Assessing Polysubstance Use of Licit (Gabapentin, Xylazine) and Illicit Substances

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OUTLINE: Polysubstance Use

- What is it?
- How common is it?
- Why do we care about it?
- What are some of the hurdles in studying it?
Polysubstance Use: What is it?

**Timeframe**
- Concurrent: Use of different drugs on separate occasions
- Simultaneous: Co-ingestion of different drugs at the same time

**Reasons**
- Experiment
- Experience a different high
- Boost the high
- “Take the edge off”
- Relieve pain
- Relieve withdrawal
Alcohol Use Disorder (AUD) and Illicit Drug Use Disorder (IDUD) in the Past Year among People Aged 12 or Older with Past Year Substance Use Disorder (SUD):

2018

20.3 Million People Aged 12 or Older with Past Year SUD
Patients with OUD receiving care from the US Veterans Health Administration

- OUD only: 41.2%, n=27,078
- OUD + 1 other SUD: 22.9%, n=15,075
- OUD + >2 other SUDs: 35.9%, n=23,588

Lin et al. 2020 Addiction 116, 96-104
Polysubstance Use: How common is it?

URINE DRUG TESTING

Study funded by BioXcel Therapeutics
(Unpublished data; sites located in New York, New Jersey, and Florida)

What about testing for licit substances, like xylazine or gabapentin? Rapid tests are generally not available and specialized tests (HPLC, GC/MS) are expensive and slow.
Simultaneous polydrug-using college students show more impairments

## Table 2. Past-year alcohol use-related consequences based on polydrug use status

<table>
<thead>
<tr>
<th>Past-year alcohol use-related consequences</th>
<th>Past-year simultaneous polydrug users (n = 309), %</th>
<th>Past-year concurrent polydrug users (n = 235), %</th>
<th>AOR(^a) (95% CI)</th>
<th>AOR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed poorly on a test or important project</td>
<td>27.6</td>
<td>15.4</td>
<td>1.83(^*) (1.14-2.94)</td>
<td>1.57(^#) (0.98-2.51)</td>
</tr>
<tr>
<td>Missed class or work because of drinking</td>
<td>65.7</td>
<td>40.7</td>
<td>2.26(^#) (1.50-3.38)</td>
<td>1.92(^#) (1.26-2.92)</td>
</tr>
<tr>
<td>Driven a car while under the influence of alcohol</td>
<td>55.9</td>
<td>31.8</td>
<td>2.25(^#) (1.50-3.37)</td>
<td>1.97(^#) (1.29-2.99)</td>
</tr>
<tr>
<td>Driven a car after drinking 5 or more drinks in 2 hours</td>
<td>31.4</td>
<td>12.4</td>
<td>2.64(^#) (1.56-4.49)</td>
<td>2.36(^#) (1.38-4.04)</td>
</tr>
<tr>
<td>Been hurt or injured after drinking</td>
<td>40.8</td>
<td>27.4</td>
<td>1.48 (0.97-2.25)</td>
<td>1.27 (0.83-1.95)</td>
</tr>
<tr>
<td>Vomited</td>
<td>83.6</td>
<td>64.7</td>
<td>2.33(^#) (1.47-3.68)</td>
<td>1.85(^*) (1.14-3.03)</td>
</tr>
<tr>
<td>Were taken advantage of sexually</td>
<td>18.3</td>
<td>13.7</td>
<td>1.18 (0.70-1.99)</td>
<td>1.07 (0.63-1.81)</td>
</tr>
<tr>
<td>Took advantage of another sexually</td>
<td>7.6</td>
<td>3.7</td>
<td>1.83 (0.84-4.01)</td>
<td>1.76 (0.80-3.92)</td>
</tr>
<tr>
<td>Seriously thought about suicide</td>
<td>8.1</td>
<td>3.8</td>
<td>1.71 (0.72-4.04)</td>
<td>1.62 (0.69-3.80)</td>
</tr>
<tr>
<td>Were afraid you were an alcoholic</td>
<td>19.1</td>
<td>11.0</td>
<td>1.53 (0.89-2.62)</td>
<td>1.36 (0.80-2.33)</td>
</tr>
<tr>
<td>Annoyed by people criticizing your drinking</td>
<td>24.2</td>
<td>23.2</td>
<td>1.07 (0.69-1.66)</td>
<td>1.00 (0.64-1.57)</td>
</tr>
<tr>
<td>Had a drink in the morning as an eye-opener</td>
<td>19.4</td>
<td>8.9</td>
<td>2.02(^*) (1.11-3.62)</td>
<td>1.80(^#) (0.98-3.33)</td>
</tr>
<tr>
<td>Felt guilt or remorse after drinking</td>
<td>42.8</td>
<td>39.4</td>
<td>1.18 (0.80-1.74)</td>
<td>1.08 (0.92-1.26)</td>
</tr>
<tr>
<td>Felt you should cut down your drinking</td>
<td>45.0</td>
<td>34.1</td>
<td>1.19 (0.93-2.06)</td>
<td>1.20 (0.80-1.81)</td>
</tr>
<tr>
<td>Had unplanned sex</td>
<td>39.2</td>
<td>20.8</td>
<td>2.08(^#) (1.34-3.22)</td>
<td>1.81(^#) (1.15-2.84)</td>
</tr>
<tr>
<td>Had blackouts</td>
<td>58.5</td>
<td>36.7</td>
<td>2.16(^#) (1.45-3.20)</td>
<td>1.86(^#) (1.24-2.80)</td>
</tr>
<tr>
<td>CAGE instrument (positive on two or more items)</td>
<td>41.0</td>
<td>30.7</td>
<td>1.41 (0.95-2.10)</td>
<td>1.30 (0.87-1.94)</td>
</tr>
</tbody>
</table>

Notes: AOR = adjusted odds ratio; 95% CI = 95% confidence interval for the AOR. \(^a\)AOR are adjusted for all other predictors in the model and the reference group for each model was past-year concurrent polydrug use; all of the models also included gender, race/ethnicity, age of alcohol onset, and fraternity/sorority membership; the odds ratio for these variables were not shown; \(^b\)these models also controlled for frequency of past 12-month alcohol use.

\(^*\)p = .06; \(^\#\)p < .05; \(^\#\)p < .01.

McCabe et al. 2006
JStud Alc 67:529-537
Polysubstance Use: Why do we care?

OVERDOSE DATA

Most Overdose Deaths Involve One or More Illicit Drugs

The 10 most frequently occurring opioid and stimulant combinations accounted for 76.9% of overdose deaths.

Polysubstance use is associated with a greater risk of non-fatal overdose.

Prospective 2-year study of 661 PWID - 17% (n=115) reported a non-fatal OD.

**Figure 1.** Kaplan–Meier curves for time to non-fatal overdose by polysubstance use categories, 2-year follow-up.
Polysubstance Use: Why do we care?

PROSPECTIVE STUDIES: TREATMENT

Treatment outcomes are poorer among polysubstance users

**Methadone**
Problem drinkers had:
- > opioid+ urines
- > depression/anxiety
- > criminal activity

Marcovici et al. 1980
JNervMent Dis 168: 556-558

**Buprenorphine**
Active alcohol users were:
- More likely to relapse

Ferri et al. 2014
Am JAddict 23, 62-67
Gabapentin as a Potential Treatment for Co-use of Opioids and Alcohol: Human Laboratory Study

Castillo et al. 2022
RATIONALE FOR TESTING GABAPENTIN

- Inhibits the $\alpha 2\delta$ subunit of presynaptic $\text{Ca}^{2+}$ channels, which may indirectly modulate $\gamma$-aminobutyric acid (GABA) and perhaps glutamate neurotransmission (Sills, 2006)
- Good safety and tolerability profile and is in widespread clinical use for several indications (seizures, neuralgia, pain, anxiety, sleep disorders)
- Gabapentin (0, 900, and 1800 mg/day) increased rates of complete abstinence from alcohol in alcohol-dependent patients and it improved mood, sleep and craving (Mason et al., 2014); it also reduced alcohol withdrawal symptoms (Malcolm et al., 2007; Mason et al., 2009)
- In rodent models, gabapentin prevented the development of morphine-induced conditioned place preference and blocked morphine-induced dopamine release in the nucleus accumbens (Andrews et al., 2001)
METHODS

- 8-week, inpatient, within-subjects study
- Non-treatment-seeking participants with OUD and AUD
- Must use opioids and alcohol simultaneously
- Morphine maintenance dose: 30 mg QID
- Gabapentin maintenance doses: 0 and 1800 mg/day
- 9 test doses (randomized, double-blind oral solutions):
  - Placebo (0 g/kg alcohol + 0 mg/70 kg oxycodone)
  - 0.5 g/kg alcohol
  - 0.75 g/kg alcohol
  - 0.5 g/kg alcohol + 0 mg/70 kg oxycodone
  - 0.5 g/kg alcohol + 30 mg/70 kg oxycodone
  - 0.5 g/kg alcohol + 15 mg/70 kg oxycodone
  - 0.75 g/kg alcohol + 30 mg/70 kg oxycodone
  - 0.75 g/kg alcohol + 15 mg/70 kg oxycodone
- PRIMARY DEPENDENT MEASURE: Visual analog scale rating of Drug Liking
- SECONDARY DEPENDENT MEASURES: Other VAS, physiological responses

<table>
<thead>
<tr>
<th>1st MAINTENANCE DOSE (0 or 1800 mg/day Gabapentin)</th>
<th>Test Week 1</th>
<th>Test Week 2</th>
<th>Test Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilization on morphine and the first dose of study medication</td>
<td>Mon</td>
<td>Tue</td>
<td>Wed</td>
</tr>
<tr>
<td>Oxy (mg/70kg)</td>
<td>0</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Alcohol (g/kg)</td>
<td>0</td>
<td>High</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd MAINTENANCE DOSE (1800 or 0 mg/day Gabapentin)</th>
<th>Test Week 4</th>
<th>Test Week 5</th>
<th>Test Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilization on the second dose of study medication</td>
<td>Mon</td>
<td>Tue</td>
<td>Wed</td>
</tr>
<tr>
<td>Oxy (mg/70kg)</td>
<td>15</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol (g/kg)</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
DEMOGRAPHICS of COMPLETERS (n=13)

- 12 men, 1 woman
- 44.1 ± 3.0 years of age
- 8 Black, 3 White, 2 Hispanic
- 10 IN heroin user, 3 IV and IN heroin user
- 6.6 ± 0.3 days per week heroin (range: 4-7 days)
- 7.6 ± 0.9 bags per day heroin
- 5.6 ± 0.5 days per week alcohol (range: 3-7 days)
- 5.3 ± 0.6 drinks per occasion (range: 2-9 drinks)
- 4 discontinued early: 2 for personal reasons, 2 for elevated blood pressure
Does GABAPENTIN alter the abuse liability of oxycodone and alcohol, alone or in combination?
Alcohol significantly increased Liking.

Oxycodone did not affect Liking.

Oxycodone did not affect Liking.

Main Effect of Gabapentin Dose:
Alcohol Dose: p=0.04

Gabapentin Dose (PO):
- 0 mg QD
Overall gabapentin significantly increased liking. But it appeared to increase liking of oxycodone alone. Overall, gabapentin did not affect liking.
Overall gabapentin significantly increased ratings of High.

But it appeared to increase ratings of High with oxycodone alone.

Gabapentin alone did not affect ratings of High.

Overall gabapentin significantly increased ratings of High.
Overall gabapentin significantly increased ratings of Sedated.

But it appeared to increase oxycodone-induced ratings of Sedated.

Gabapentin alone did not affect ratings of Sedated.

Overall gabapentin significantly increased ratings of Sedated.
But overall gabapentin increased the amount subjects would pay for the drugs.

Unlike the other effects, it did not affect the amount they would pay for oxycodone alone.

Gabapentin alone did not affect the amount subjects would pay for the drugs.

Main Effect of Gabapentin Dose: p=0.06
Alcohol Dose: p=0.03

Gabapentin Dose (PO)
- 0 mg QD
- 1800 mg QD
Similar findings were observed for ratings of potency
Similar findings also were observed for ratings of high quality.
WHAT ABOUT POTENTIAL TOXIC EFFECTS OF THE COMBINATION?
Oxycodone decreased oxygen saturation.

Alcohol also decreased oxygen saturation.
Gabapentin did not significantly alter oxygen saturation.
Gabapentin did not significantly alter respiratory rate.
Gabapentin did not significantly alter end tidal CO₂.
CONCLUSIONS

Gabapentin increases the abuse liability of alcohol and the combination of alcohol and oxycodone.

Under the current experimental conditions, there is little evidence that gabapentin increases the risk of respiratory depression.

Implications for treatment...
Xylazine + Fentanyl: “Emerging Threat”

- “Tranq”, “anestesia de caballo”
- Alpha 2 adrenergic agonist used as a sedative and anesthetic in veterinary medicine
- Anesthetic dose (0.2-1 mg/kg IV or IM)
- Onset of effects (1-2 min)
- Time to peak effect (30 min)
- Duration of action (4 hours)
- Online purchase: $6-20 per kg
- Fentanyl has a short duration of action so xylazine may be used to prolong its effects
- Can cause severe wounds
Gupta et al, NEJM, 2023
DOI: 10.1056/NEJMp2303120
SURVEY and URINE DRUG SCREENS

Have you heard of xylazine/tranq? (yes/no)

- October: 0/10
- November: 6/57
- December: 8/50
- January: 4/50
- February: 4/16
- March: 5/20
- April: 24/27

Have you ever used xylazine? (yes/no/not sure)

- 32% of urine samples positive for xylazine (25/78)

- October: 0/10
- November: 4/57
- December: 5/50
- January: 1/50
- February: 2/16
- March: 2/20
- April: 11/36
CONCLUSIONS

- Converging data (overdose deaths, drug seizures, surveys, urine drug testing) suggest that xylazine is increasingly found in illicit drug supplies.

- Unanswered questions:
  - What is the abuse liability of xylazine itself?
  - Does xylazine increase the likelihood of drug overdose deaths?
  - What is the mechanism of the severe wounds that are observed in people using drugs mixed with xylazine?
  - What are the characteristics of xylazine physical dependence and withdrawal?
  - How do we treat the wounds/withdrawal symptoms?

- Clinical research hurdles:
  - Not approved for human use, so no data to support an IND
  - Urine drug tests only recently became available (not CLIA waived)
  - A LOT OF WORK NEEDS TO BE DONE!
Thank you!

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