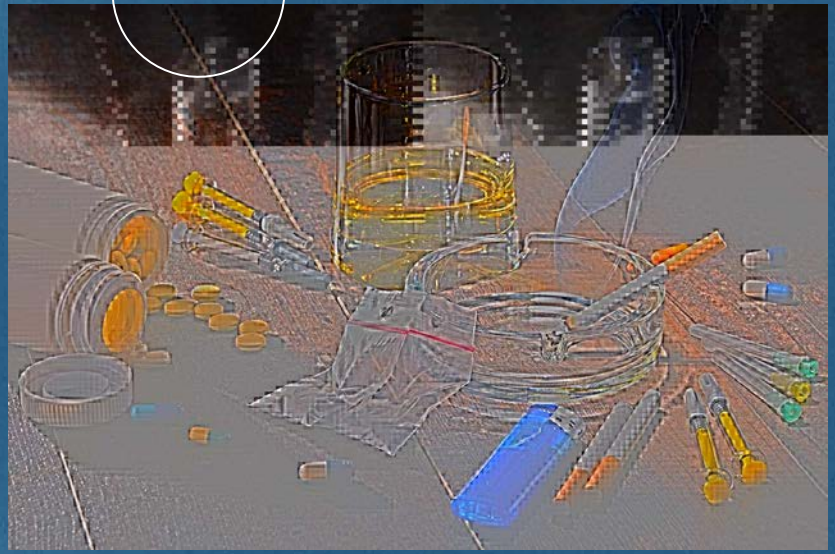


Assessing Polysubstance Use of Licit (Gabapentin, Xylazine) and Illicit Substances

Sandra D Comer, PhD
Professor of Neurobiology
(in Psychiatry)
Columbia University & NYSPI

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

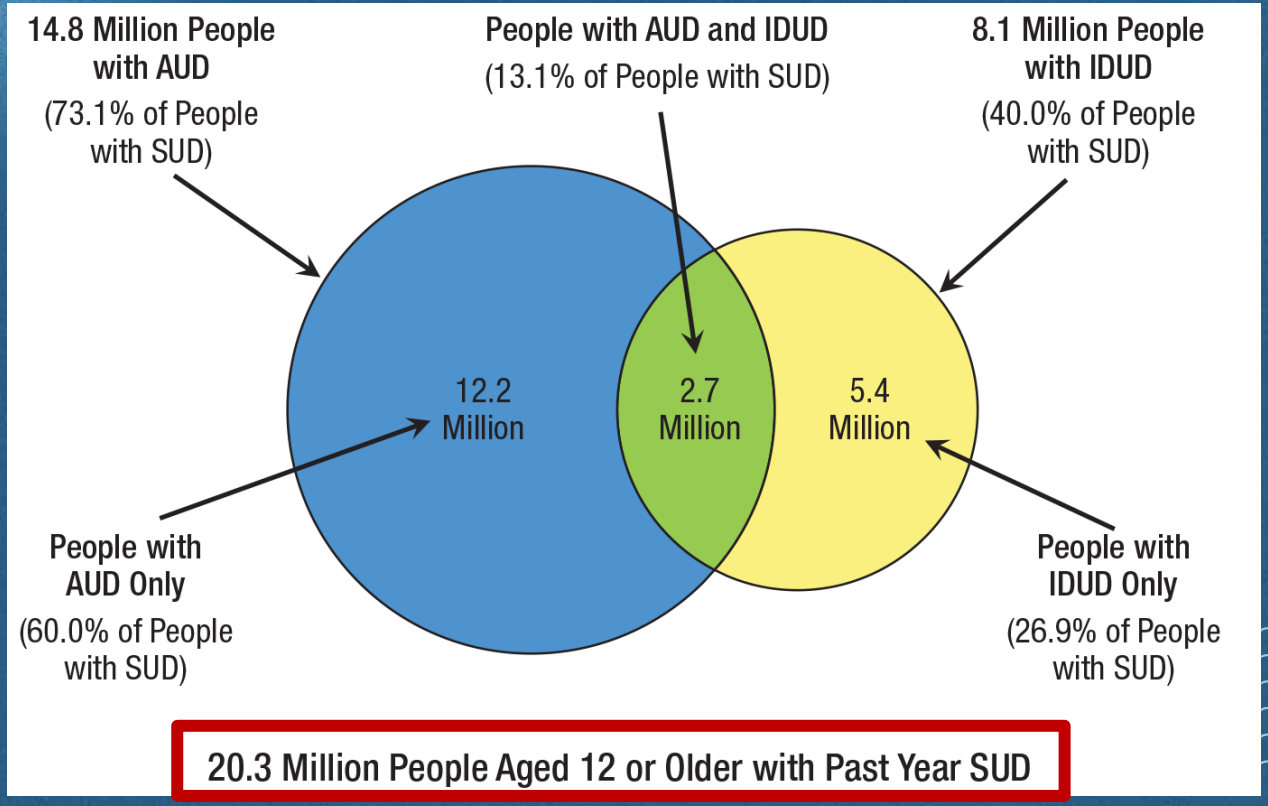
Simultaneous:
Co-ingestion of different drugs at the same time

Reasons

- Experiment
- Experience a different high
- Boost the high
- “Take the edge off”
- Relieve pain
- Relieve withdrawal

Polysubstance Use: How common is it?

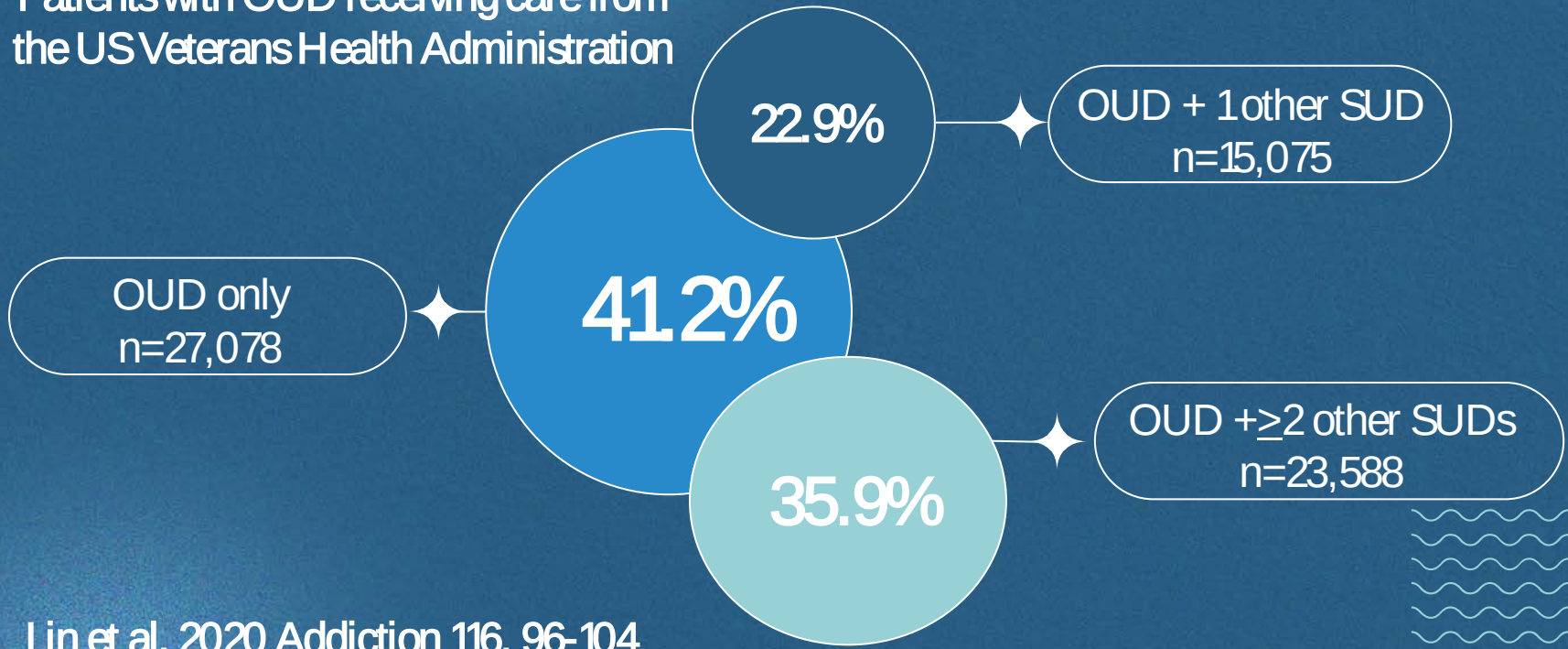
Alcohol Use Disorder (AUD) and Illicit Drug Use Disorder (IDUD) in the Past Year among People Aged 12 or Older with Past Year Substance Use Disorder (SUD): 2018



NSDUH Briefing 2018

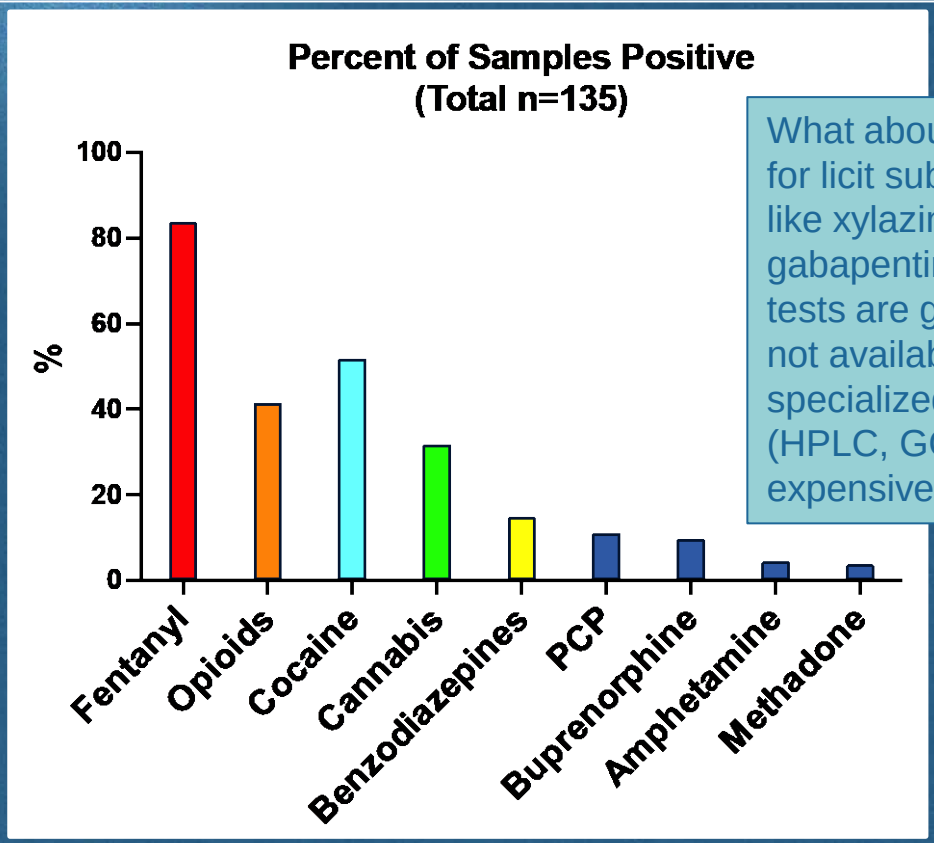
Polysubstance Use: How common is it?

Patients with OUD receiving care from the US Veterans Health Administration



Lin et al. 2020 Addiction 116, 96-104

Polysubstance Use: How common is it?
URINE DRUG TESTING



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.

Study funded by BioXcel Therapeutics (Unpublished data; sites located in New York, New Jersey, and Florida)

Polysubstance Use: Why do we care? SURVEYS

Simultaneous polydrug-using college students show more impairments

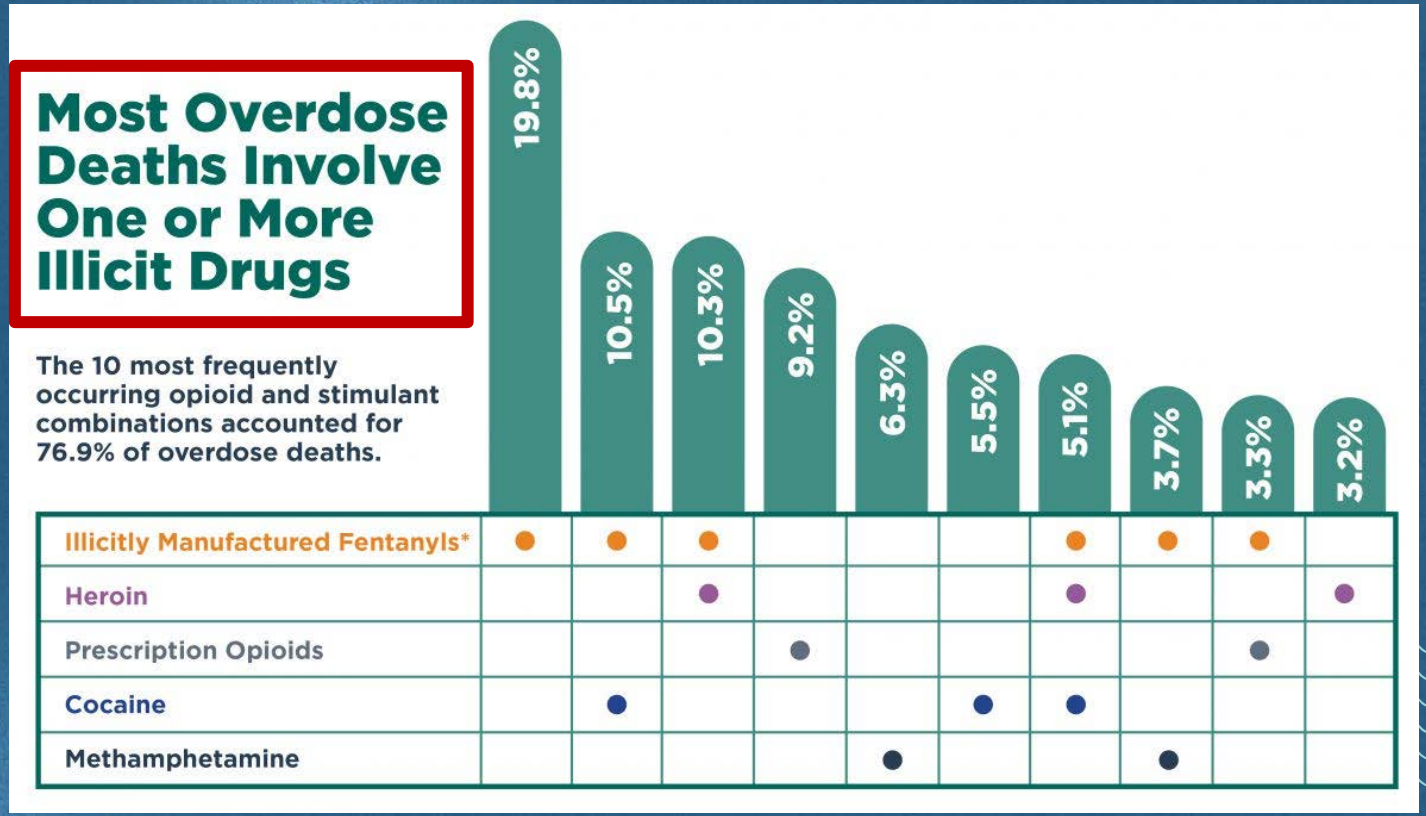
TABLE 2. Past-year alcohol use-related consequences based on polydrug use status

Past-year alcohol use-related consequences	Past-year simultaneous polydrug users (n = 309), %	Past-year concurrent polydrug users (n = 235), %	AOR[a] (95% CI)	AOR[b] (95% CI)
Performed poorly on a test or important project	27.6	15.4	1.83* (1.14-2.94)	1.57§ (0.98-2.51)
Missed class or work because of drinking	65.7	40.7	2.26† (1.50-3.38)	1.92† (1.26-2.92)
Driven a car while under the influence of alcohol	55.9	31.8	2.25† (1.50-3.37)	1.97† (1.29-2.99)
Driven a car after drinking 5 or more drinks in 2 hours	31.4	12.4	2.64† (1.56-4.49)	2.36† (1.38-4.04)
Been hurt or injured after drinking	40.8	27.4	1.48 (0.97-2.25)	1.27 (0.83-1.95)
Vomited	83.6	64.7	2.33† (1.47-3.68)	1.85* (1.14-3.03)
Were taken advantage of sexually	18.3	13.7	1.18 (0.70-1.99)	1.07 (0.63-1.81)
Took advantage of another sexually	7.6	3.7	1.83 (0.84-4.01)	1.76 (0.80-3.92)
Seriously thought about suicide	8.1	3.8	1.71 (0.72-4.04)	1.62 (0.69-3.80)
Were afraid you were an alcoholic	19.1	11.0	1.53 (0.89-2.62)	1.36 (0.80-2.33)
Annoyed by people criticizing your drinking	24.2	23.2	1.07 (0.69-1.66)	1.00 (0.64-1.57)
Had a drink in the morning as an eye-opener	19.4	8.9	2.02* (1.11-3.62)	1.80§ (0.98-3.33)
Felt guilt or remorse after drinking	42.8	39.4	1.18 (0.80-1.74)	1.08 (0.92-1.26)
Felt you should cut down your drinking	45.0	34.1	1.39 (0.93-2.06)	1.20 (0.80-1.81)
Had unplanned sex	39.2	20.8	2.08† (1.34-3.22)	1.81† (1.15-2.84)
Had blackouts	58.5	36.7	2.16† (1.45-3.20)	1.86† (1.24-2.80)
CAGE instrument (positive on two or more items)	41.0	30.7	1.41 (0.95-2.10)	1.30 (0.87-1.94)

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
J Stud Alc 67:529-537

Polysubstance Use: Why do we care?
OVERDOSE DATA



https://www.cdc.gov/drugoverdose/featured-topics/VS-overdose-deaths-illicit-drugs.html

Polysubstance Use: Why do we care?
PROSPECTIVE STUDIES: OVERDOSE

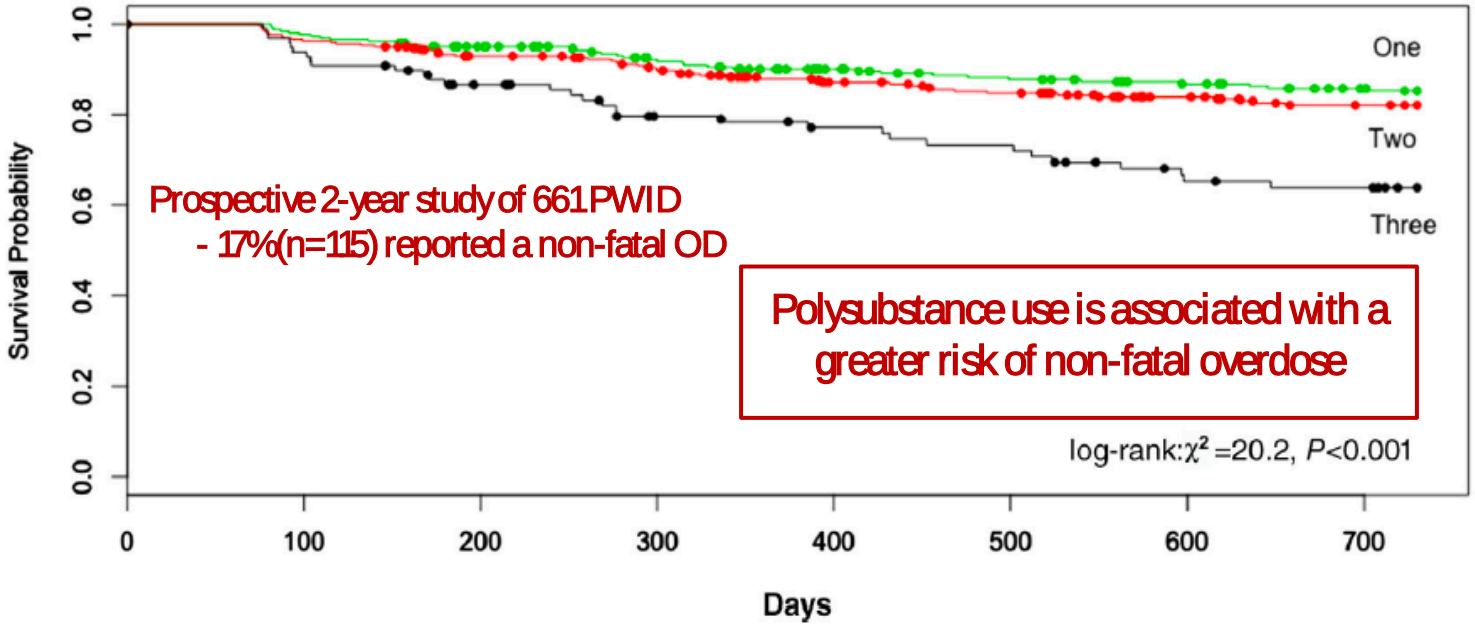


Figure 1. *Kaplan–Meier curves for time to non-fatal overdose by polysubstance use categories, 2-year follow-up.*

Rivera Saldana et al. 2021 Drug Alc Rev 40, 1340-1348

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
J Nerv Ment Dis 168: 556-558

Buprenorphine

Active alcohol users were:

- More likely to relapse

Ferri et al. 2014
Am J Addict 23, 62-67

Polysubstance Use: What can we do?
PROSPECTIVE STUDIES: HUMAN LAB

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 Ca^{2+} channels, which may indirectly modulate γ-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
  - 15 mg/70 kg oxycodone
  - 30 mg/70 kg oxycodone
  - 0.5 g/kg alcohol + 15 mg/70 kg oxycodone
  - 0.5 g/kg alcohol + 30 mg/70 kg oxycodone
  - 0.75 g/kg alcohol + 15 mg/70 kg oxycodone
  - 0.75 g/kg alcohol + 30 mg/70 kg oxycodone

- PRIMARY DEPENDENT MEASURE: Visual analog scale rating of Drug Liking
- SECONDARY DEPENDENT MEASURES: Other VAS, physiological responses

Representative Study Design

1st MAINTENANCE DOSE (0 or 1800 mg/day Gabapentin)	Test Week 1						Test Week 2					Test Week 3				
Stabilization on morphine and the first dose of study medication		Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri
	Oxy (mg/70kg)	0		30		15	15		30		0	30		15		0
	Alcohol (g/kg)	0		High		0	High		Low		High	0		Low		Low
2nd MAINTENANCE DOSE (1800 or 0 mg/day Gabapentin)	**Test Week 4**						**Test Week 5**					**Test Week 6**				
Stabilization on the second dose of study medication		Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri
	Oxy (mg/70kg)	15		30		0	30		15		0	30		0		15
	Alcohol (g/kg)	Low		High		Low	0		High		0	Low		High		0

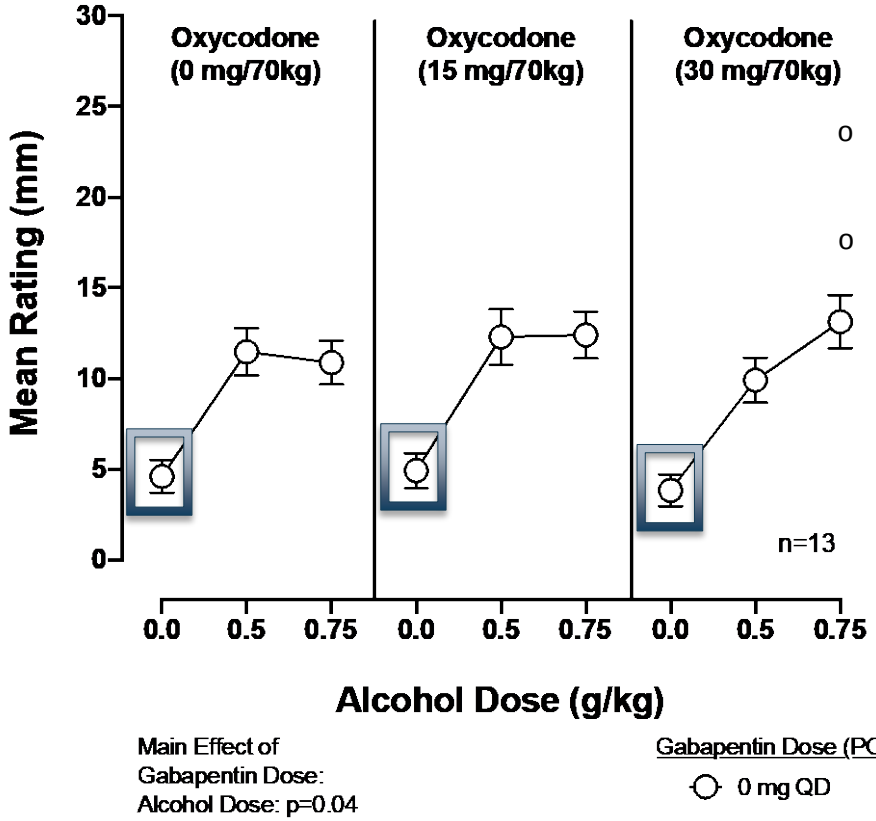
DEMOGRAPHICS of COMPLETERS (n=13)

- 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

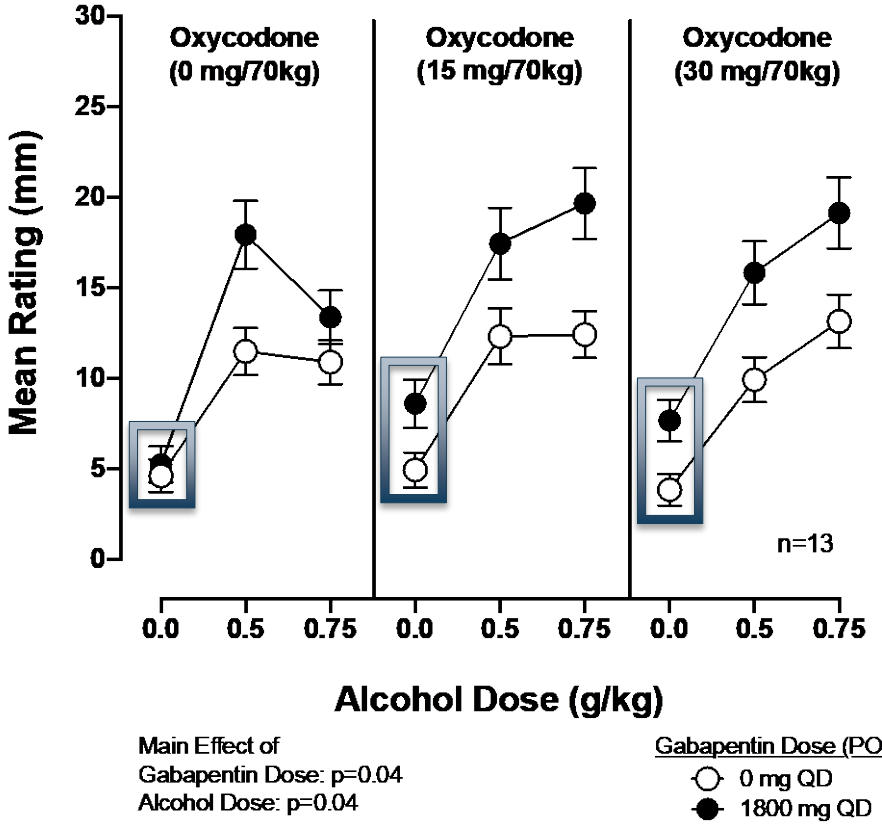
Does GABAPENTIN alter the abuse liability of oxycodone and alcohol, alone or in combination?

Liking



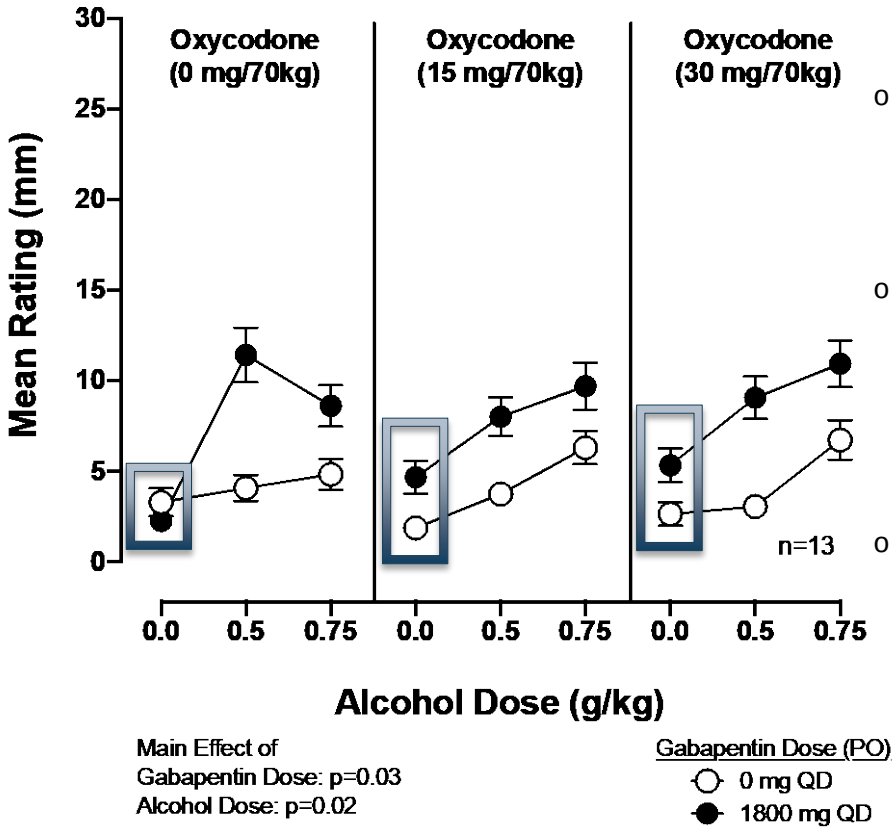
- Alcohol significantly increased Liking
- Oxycodone did not affect Liking

Liking

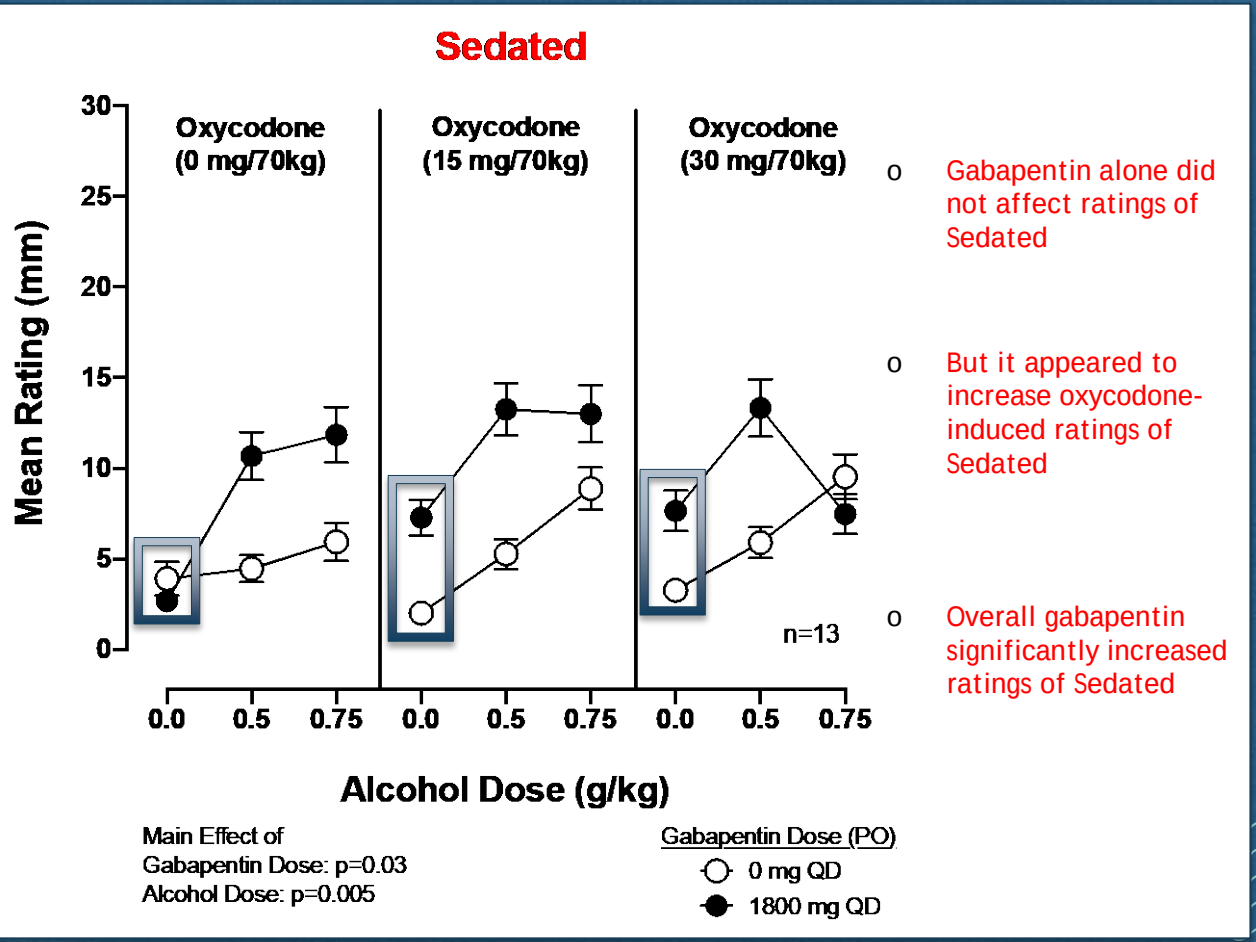


- Gabapentin alone did not affect Liking
- But it appeared to increase Liking of oxycodone alone
- Overall gabapentin significantly increased Liking

High

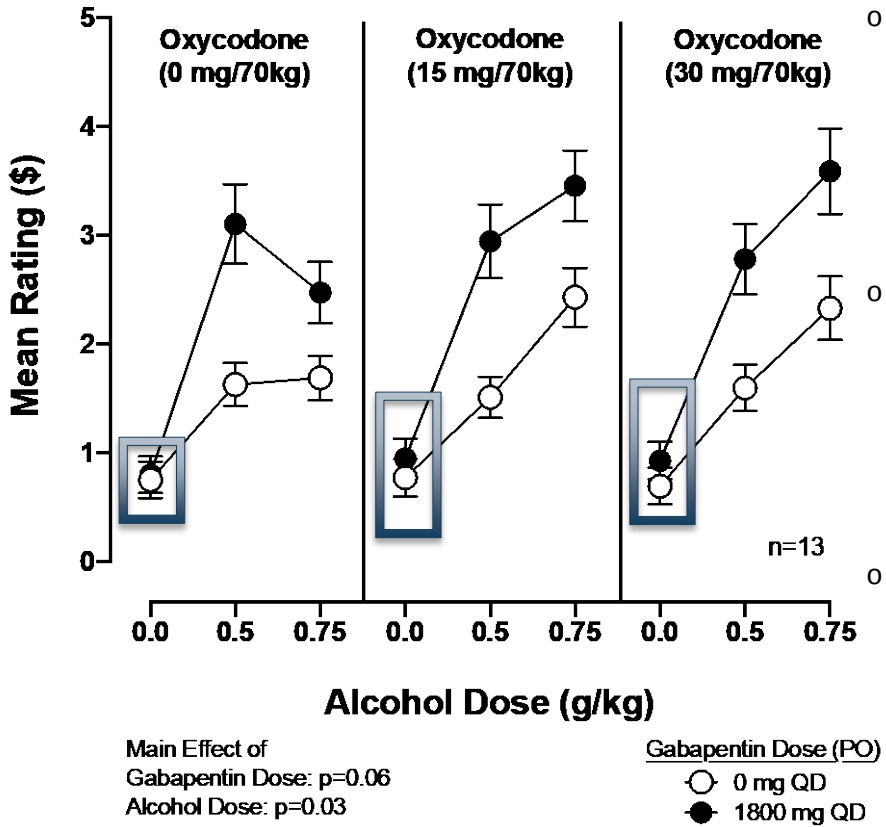


- Gabapentin alone did not affect ratings of High
- But it appeared to increase ratings of High with oxycodone alone
- Overall gabapentin significantly increased ratings of High



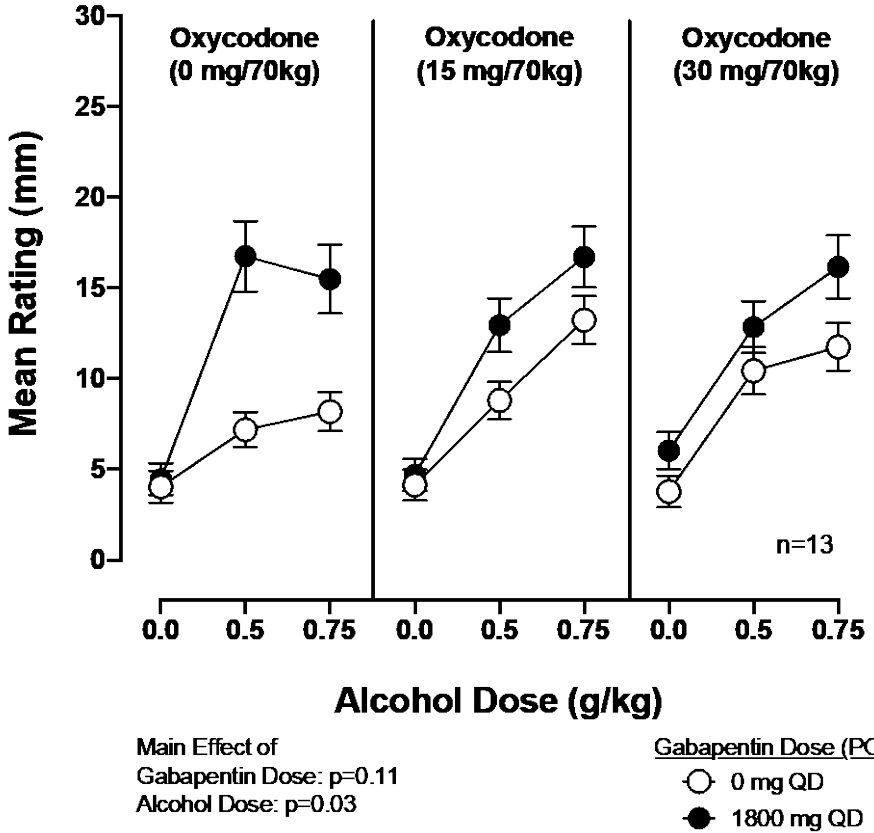
- Gabapentin alone did not affect ratings of Sedated
- But it appeared to increase oxycodone-induced ratings of Sedated
- Overall gabapentin significantly increased ratings of Sedated

Would Pay



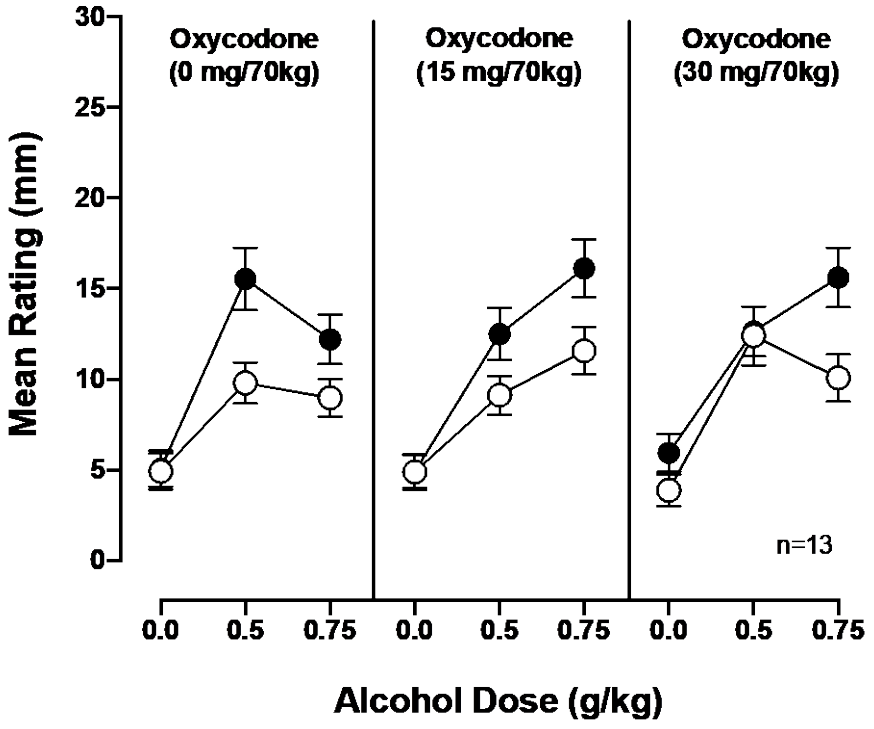
- Gabapentin alone did not affect the amount subjects would pay for the drugs
- Unlike the other effects, it did not affect the amount they would pay for oxycodone alone
- But overall gabapentin increased the amount subjects would pay for the drugs

Potent



- Similar findings were observed for ratings of potency

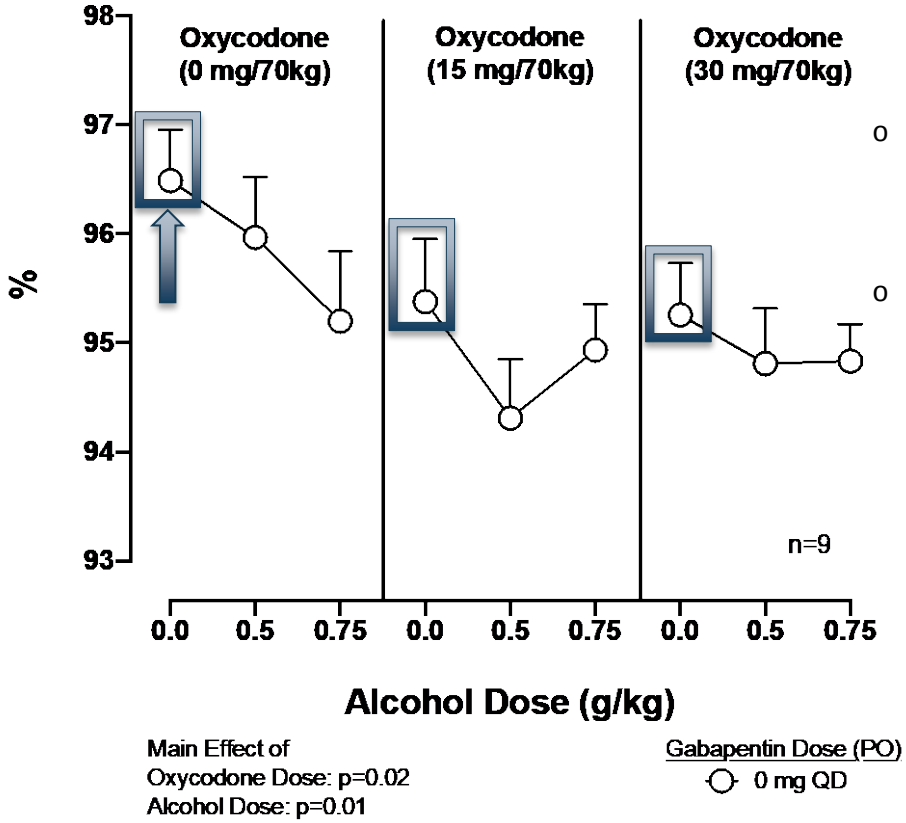
High Quality



- Similar findings also were observed for ratings of high quality

WHAT ABOUT POTENTIAL TOXIC EFFECTS OF THE COMBINATION?

Trough Oxygen Saturation

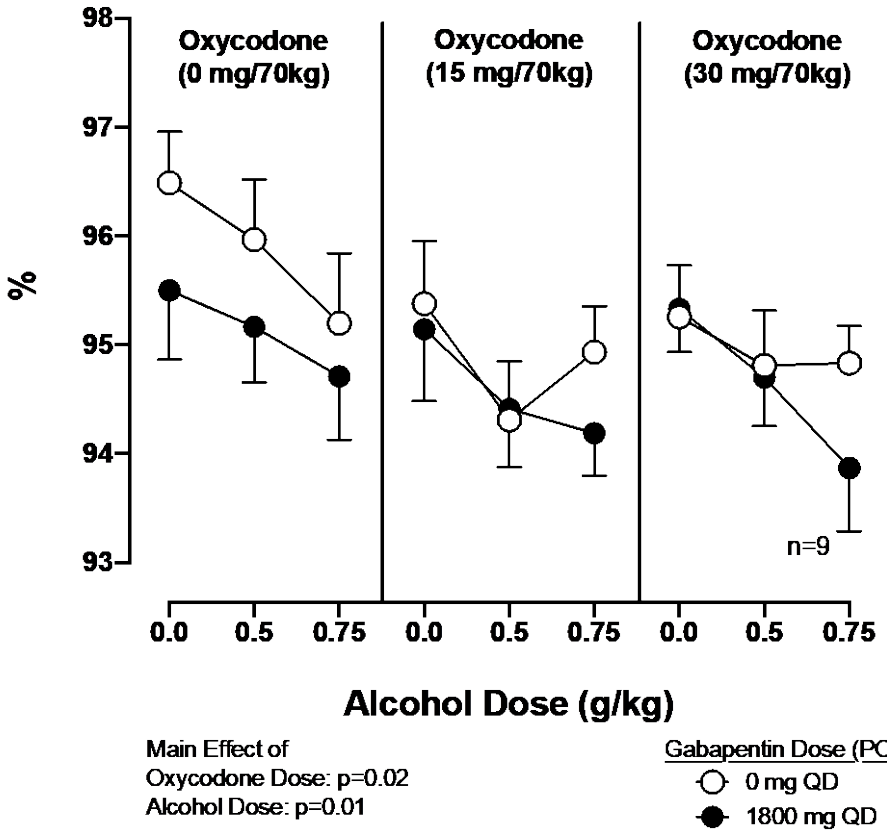


Main Effect of
Oxycodone Dose: p=0.02
Alcohol Dose: p=0.01

Gabapentin Dose (PO)
0 mg QD

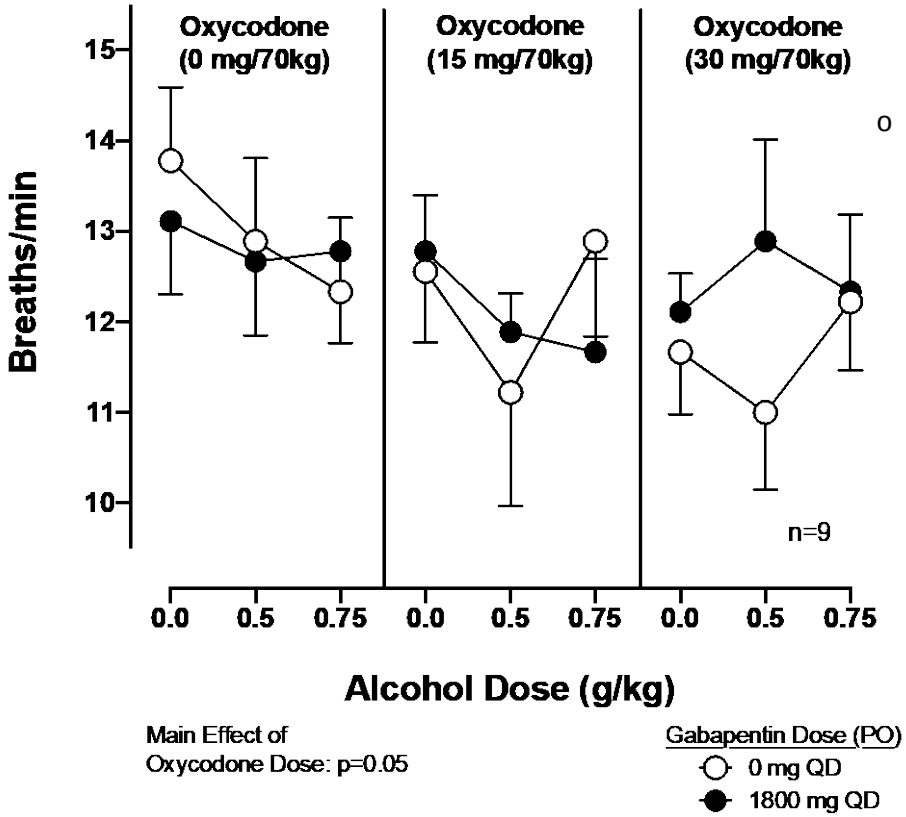
- Oxycodone decreased oxygen saturation
- Alcohol also decreased oxygen saturation

Trough Oxygen Saturation



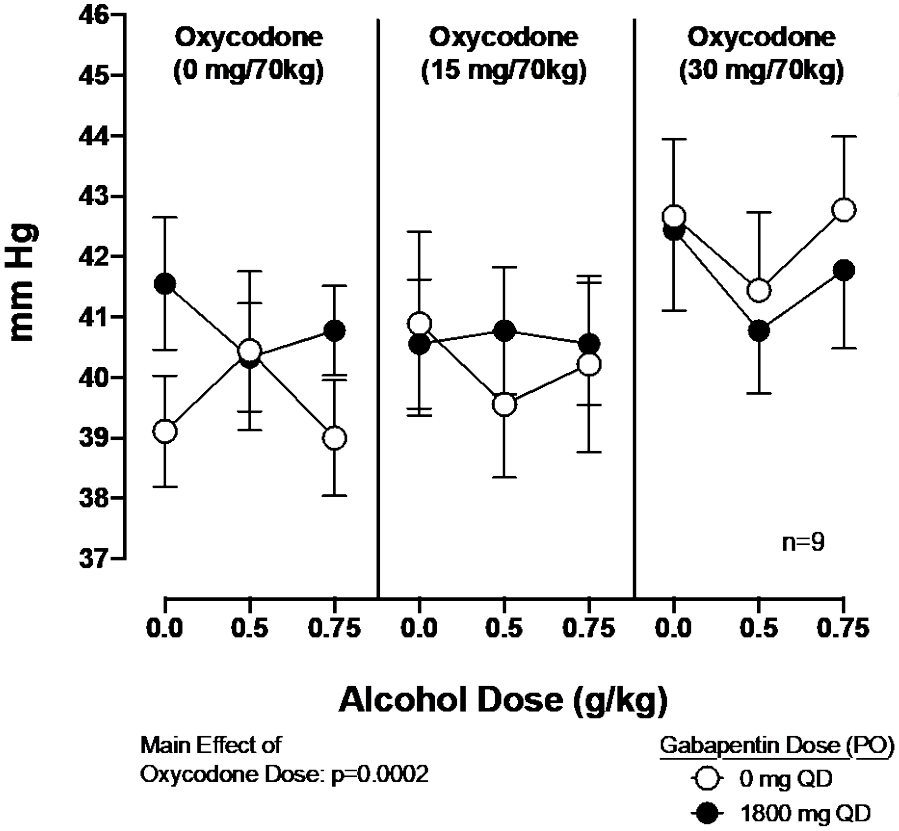
- Gabapentin did not significantly alter oxygen saturation

Trough Respiratory Rate



- Gabapentin did not significantly alter respiratory rate

Peak End Tidal CO_2



- Gabapentin did not significantly alter end tidal CO_2

CONCLUSIONS

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

REVIEW

Gabapenti
review

Rachel V. Smith[1,2]

Journal of Substance Abuse Treatment 105 (2019) 1–4

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

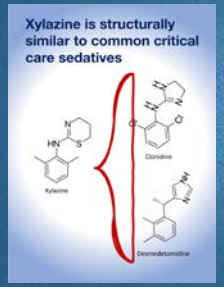
journal homepage: www.elsevier.com/locate/jsat

Gabapentin prescribed during substance abuse treatment: The perspective of treatment providers

Mance E. Buttram[a,*], Steven P. Kurtz[a], Matthew S. Ellis[b], Theodore J. Cicero[b]

[a] Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University, 7255 NE 4th Avenue, Suite 112, Miami, FL 33138, USA
[b] Washington University, Department of Psychiatry, Campus Box 8134, 600 S. Euclid Avenue, St. Louis, MO 63110, USA

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

SIL23331 N9H **DISCUSSION DRAFT** S.L.C.

118TH CONGRESS
1ST SESSION

S. _____

To prohibit certain uses of xylazine, and for other purposes.

IN THE SENATE OF THE UNITED STATES

Ms. CORTEZ MASTO introduced the following bill; which was read twice and referred to the Committee on _____

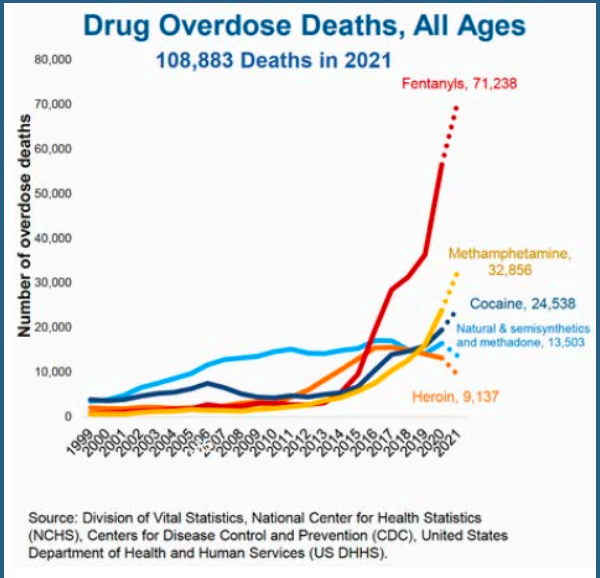
A BILL

To prohibit certain uses of xylazine, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Combating Illicit Xylazine Act".



Estimated Xylazine-Involved Drug-Poisoning Deaths in the United States, 2018–2021.

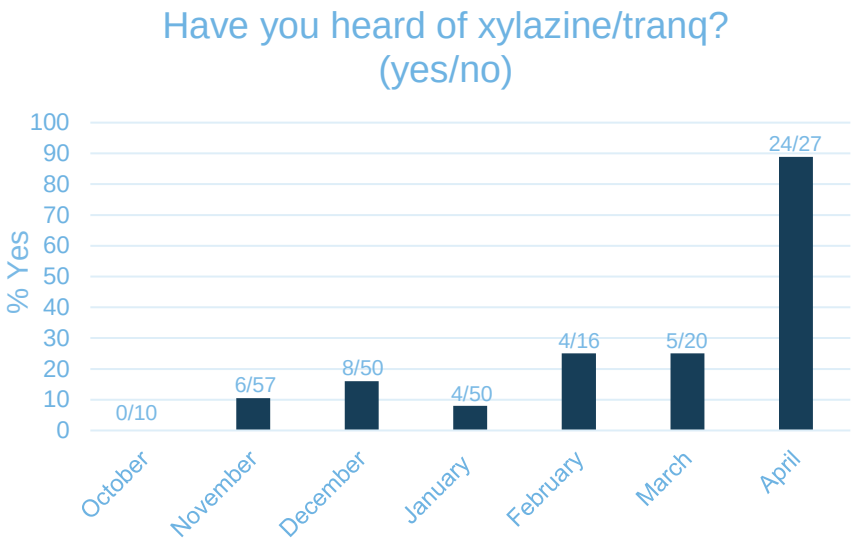
Gupta et al, NEJM, 2023
DOI: 10.1056/NEJMp2303120

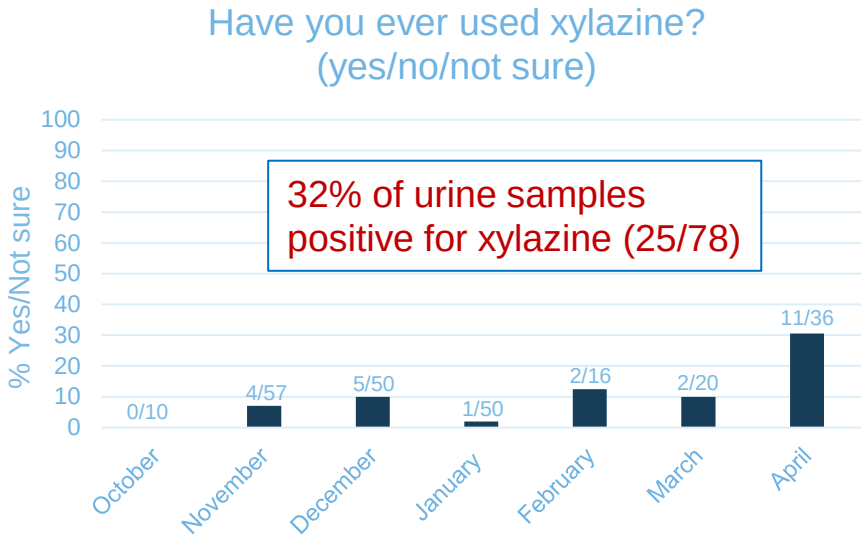
(U) Figure 1. DEA Forensic Laboratory Identifications of Xylazine by Region

Region	*2020*	*2021*	*Percent Increase*
Northeast	346	556	61%
South	198	580	193%
Midwest	110	118	7%
West	77	163	112%

Source: DEA-DCI-DIR-001-23 Unclassified

SURVEY and URINE DRUG SCREENS





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!

Jermaine Jones, PhD
Jeanne Manubay, MD
Shanthi Mogali, MD
Rob Whittington, MD
Claudia Tindall, NP
Janet Murray, RN
Gabriela Madera, BS
Vincent Woolfolk, BS
Ben Foote, BS
Nicholas Allwood, BS
Greg Cortorreal, BS
Freymon Perez, BS

Rachel Luba, PhD
Suky Martinez, PhD
Felipe Castillo, MD
Samantha Chong, BS
Rebecca Abbott, BS

Thank you to NIDA!
R01DA039169, UG3DA047711