



Neuropsychiatric Aspects of Addiction

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Disclosures

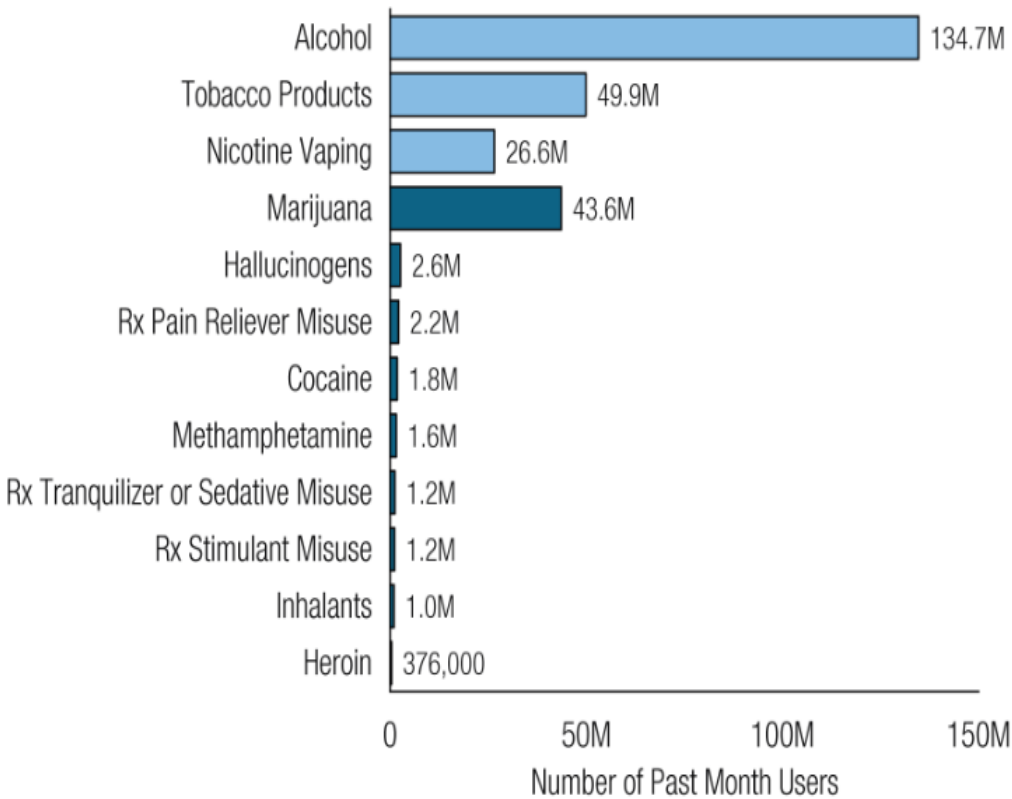
I have the following relevant financial relationships with commercial interests to disclosure:

I currently receive in-kind support in the form of medications (buprenorphine injections, Brixadi) from Braeburn to conduct a NIH-funded clinical trial (R21DA060411). I will receive research support from Apollo Therapeutics to conduct a clinical trial for a novel GLP-1RA medication. I previously received research funding from Indivior to conduct a trial of buprenorphine, which ended in August 2023.

Outline

- Addiction as a brain disease
- Neuropsychiatric manifestations of Addiction
- Neuropsychiatric co-morbidities of Addiction
- Treatment implications

Substance use remains a public health concern in the US



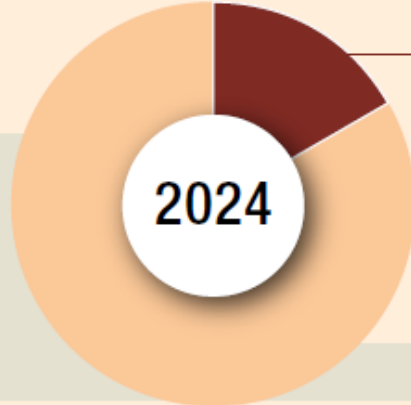
NSDUH 2025

Substance Use Disorders in the Past Year

NSDUH asked respondents aged 12 or older about the effects of their drug or alcohol use on their lives in the 12 months before the interview.

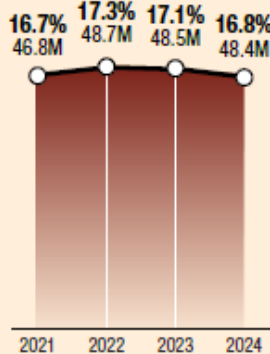


Substance Use Disorder (SUD)



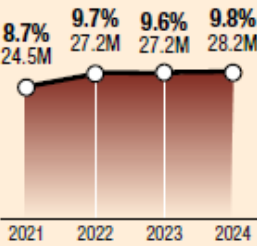
Substance Use Disorder (SUD)

Overall Trend No change



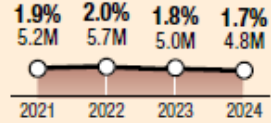
Drug Use Disorder (DUD)

Overall Trend Increased



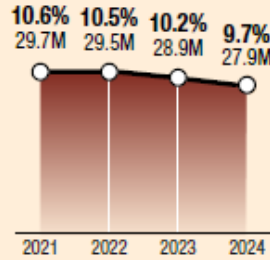
Opioid Use Disorder (OUD)

Overall Trend No change



Alcohol Use Disorder (AUD)

Overall Trend Decreased



Drug overdose deaths in the US are declining, but numbers remain high

Based on data available for analysis on: August 3, 2025

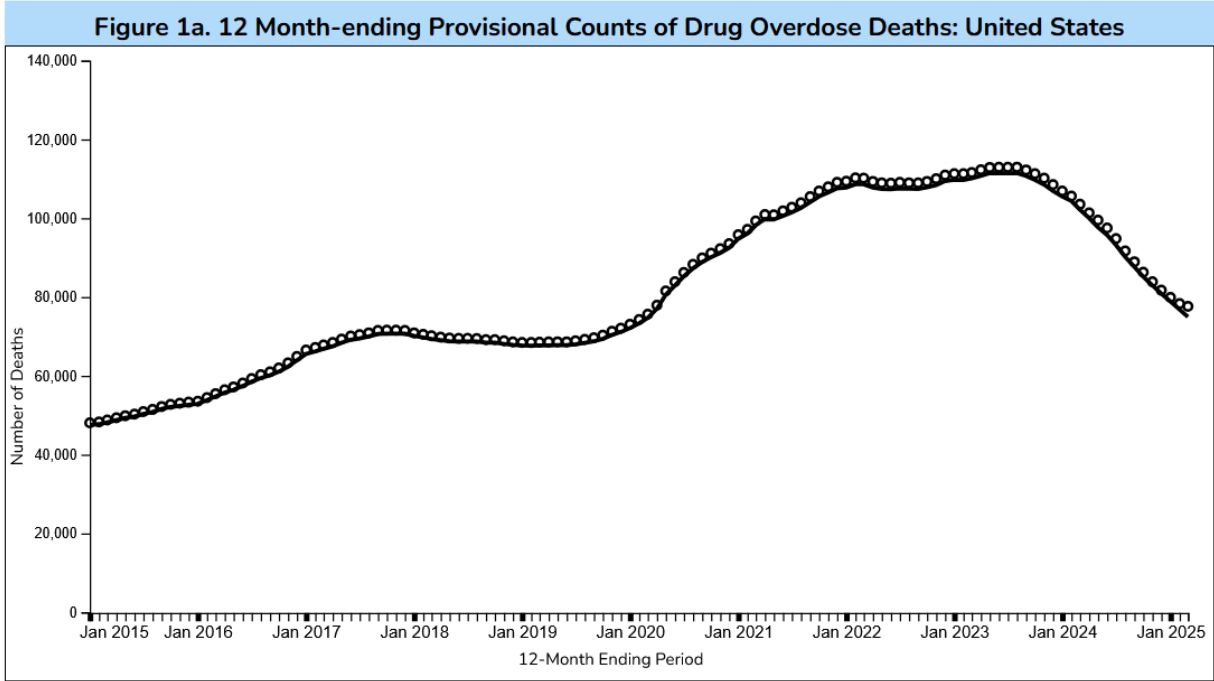
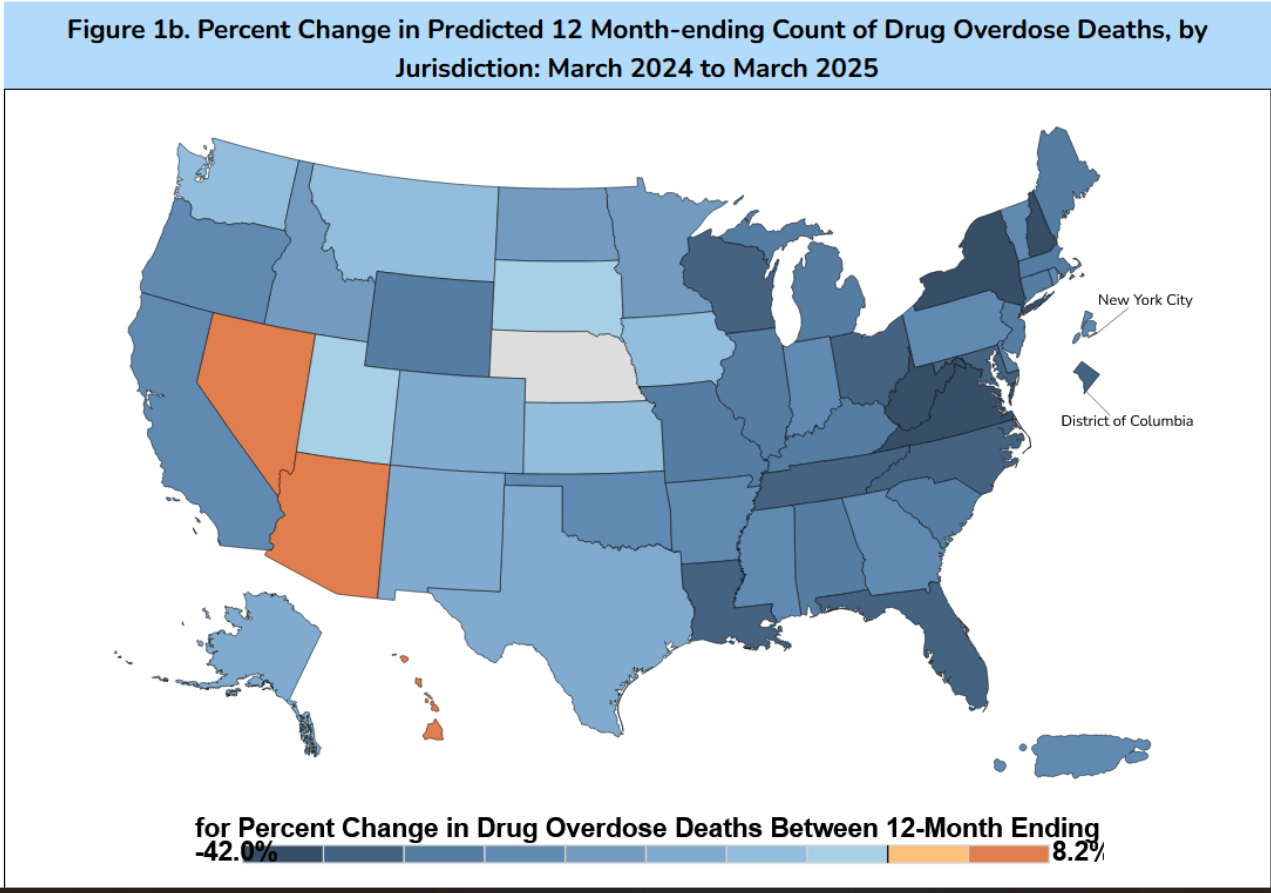
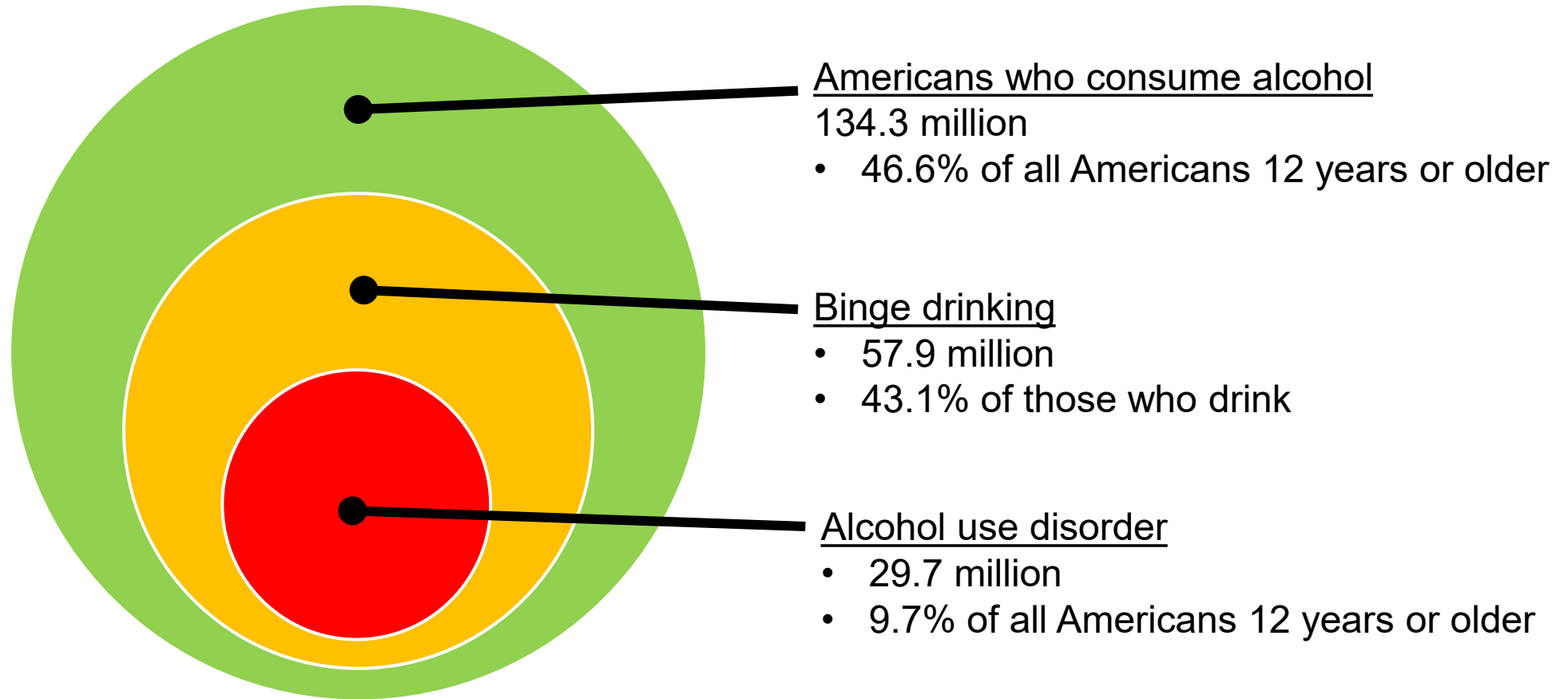


Figure 1b. Percent Change in Predicted 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: March 2024 to March 2025



Unhealthy alcohol use remains common in the US



Substance use disorder: A chronic relapsing disorder characterized by compulsive use and long-lasting brain changes...
...and the **3 Cs of addiction.**

Substance use disorder

2-3: mild

4-5: moderate

6+: severe

Tolerance
Withdrawal
Using larger amounts than intended
Persistent desire and inability to cut down
Can't stop despite knowledge of harm
Spending a lot of time using/obtaining/recovering from substance use
Cravings
Using the substance in Dangerous situations
Important social and other activities are given up for drug use
Failed role obligations
Social conflict

Physiologic dependence

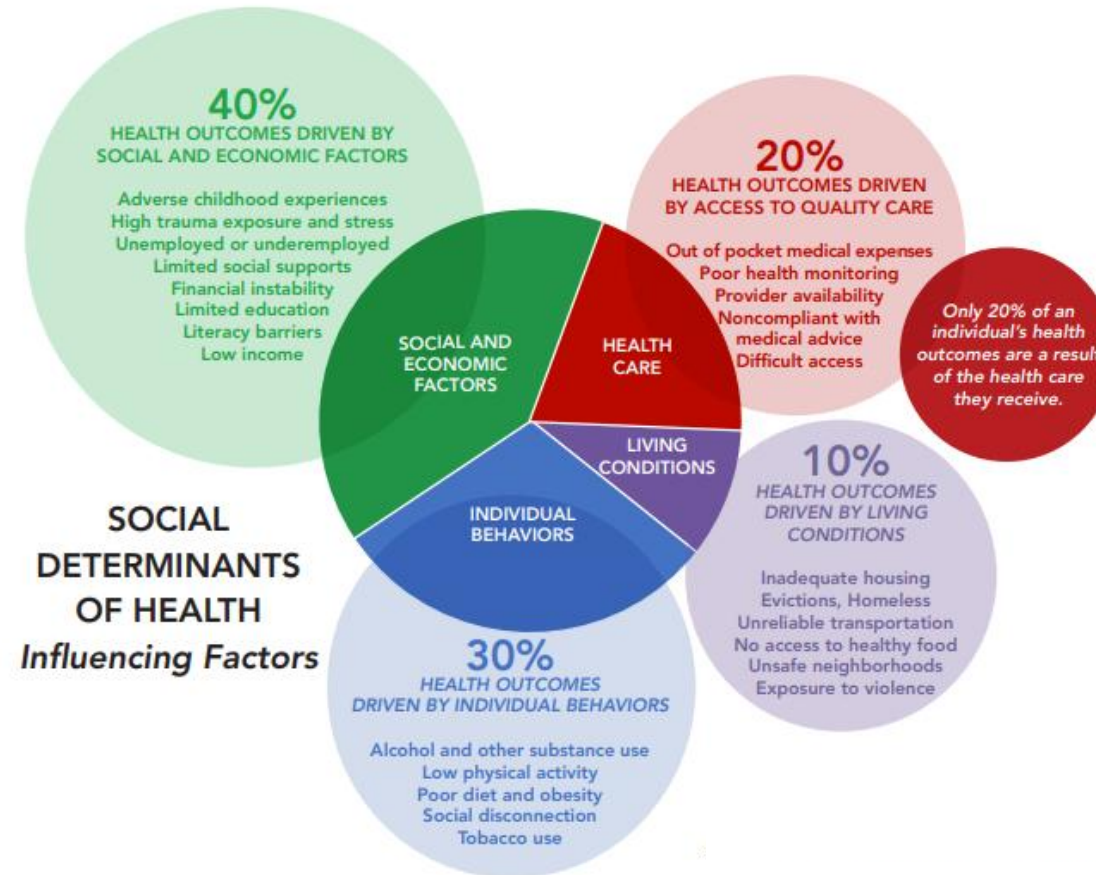
Loss of Control

Cravings

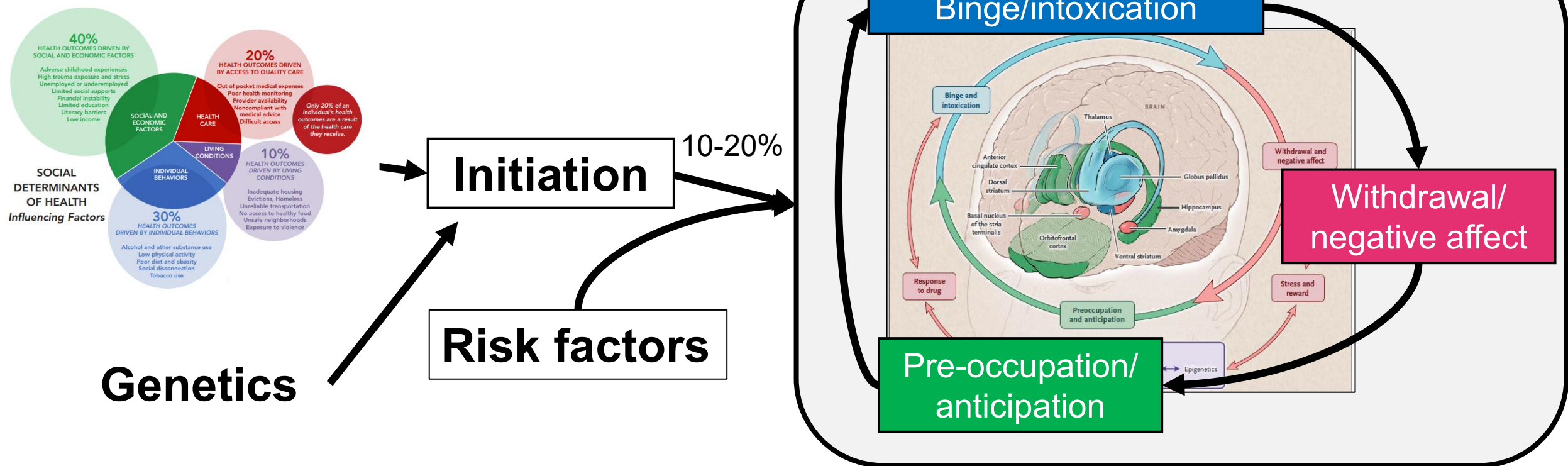
Negative Consequences

DSM5

Development of substance use disorders



Development of substance use disorders



Neurobiologic model of substance use disorders



Disrupted self-processing

- Maladaptive self-referential thoughts
- Default mode network

Self-referential
rumination



Operant Conditioning

- "Liking"
- Positive and Negative reinforcement

Binge/
intoxication



Opponent-process

- Reward vs anti-reward

Withdrawal/
Negative affect



Incentive sensitization

- "Craving"
- "Wanting"
- Triggered by cues

Pre-occupation/
Anticipation



Impaired regulation

- Poor inhibitory control
- Risk taking

Loss of control

Cravings and negative affect are elevated prior to relapse

Before and After: Craving, Mood, and Background Stress in the Hours Surrounding Drug Use and Stressful Events in Patients with Opioid-Use Disorder

Kenzie L. Preston^{*,1}, William J. Kowalczyk¹, Karran A. Phillips¹, Michelle L. Jobes¹, Massoud Vahabzadeh², Jia-Ling Lin², Mustapha Mezghanni², and David H. Epstein¹

¹Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD

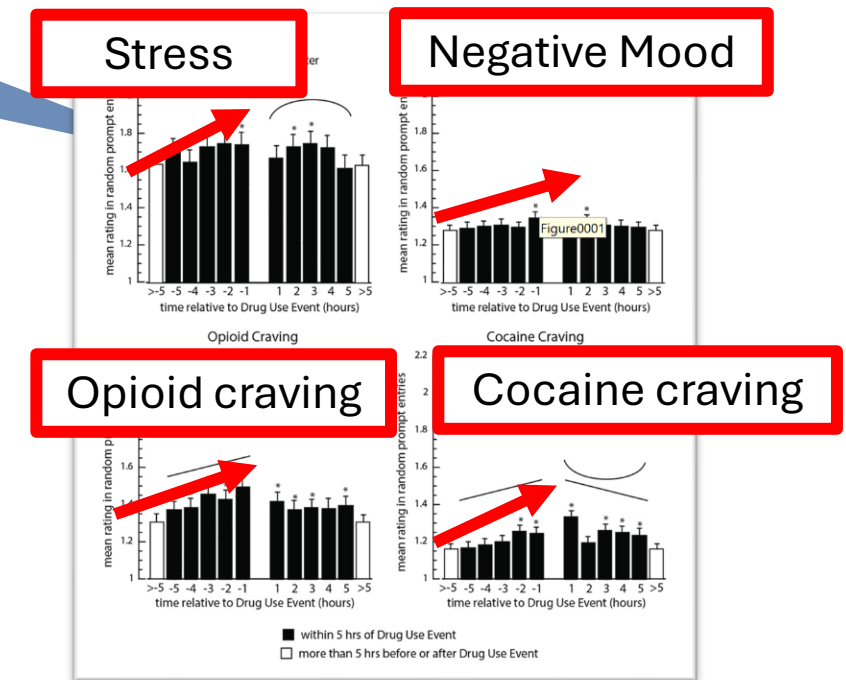
Setting: Outpatient treatment center in Baltimore

Participants: OUD patients on MOUD (n=192)

Design: 16-week prospective study

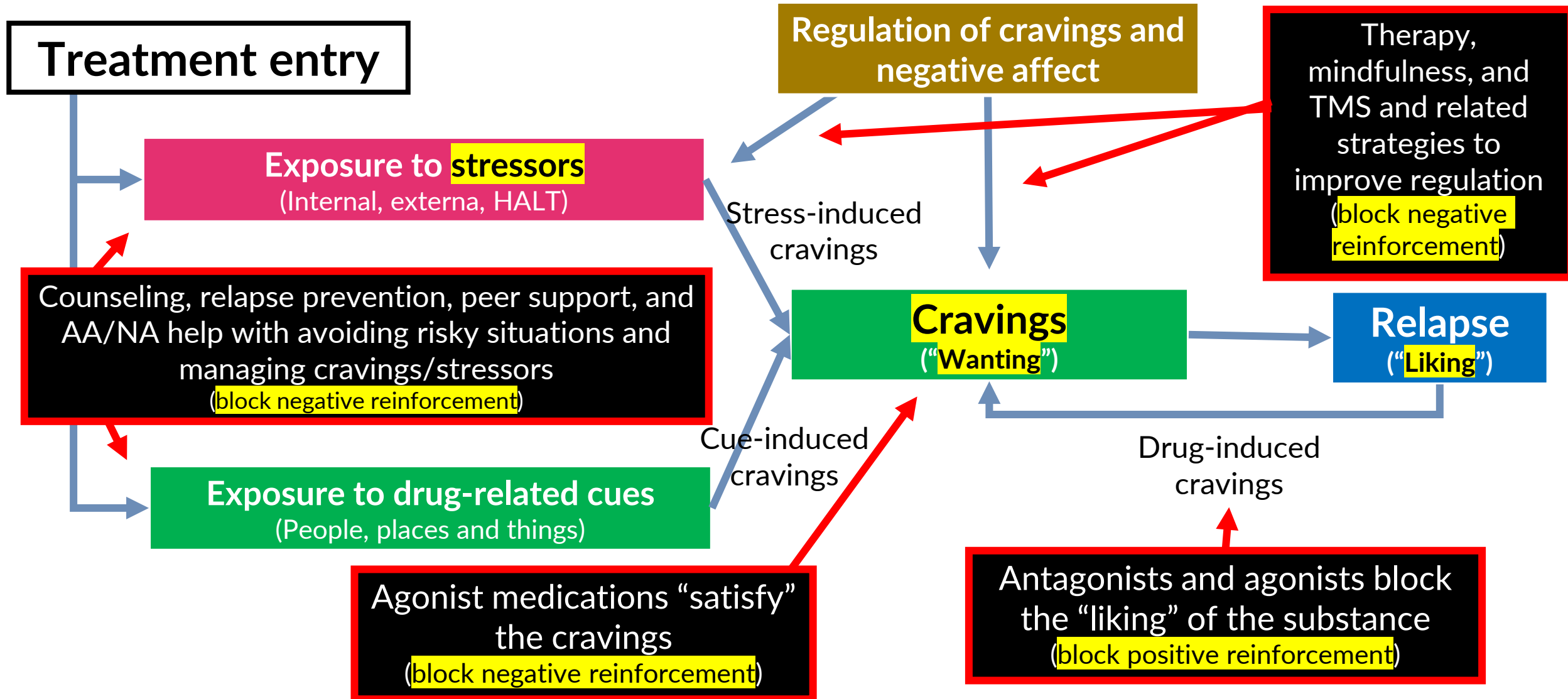
Primary outcome: Smartphone EMA report on cravings, stress, and negative mood within 5 hours before and after use

Results: Stress, cravings, and negative mood were higher prior to use events



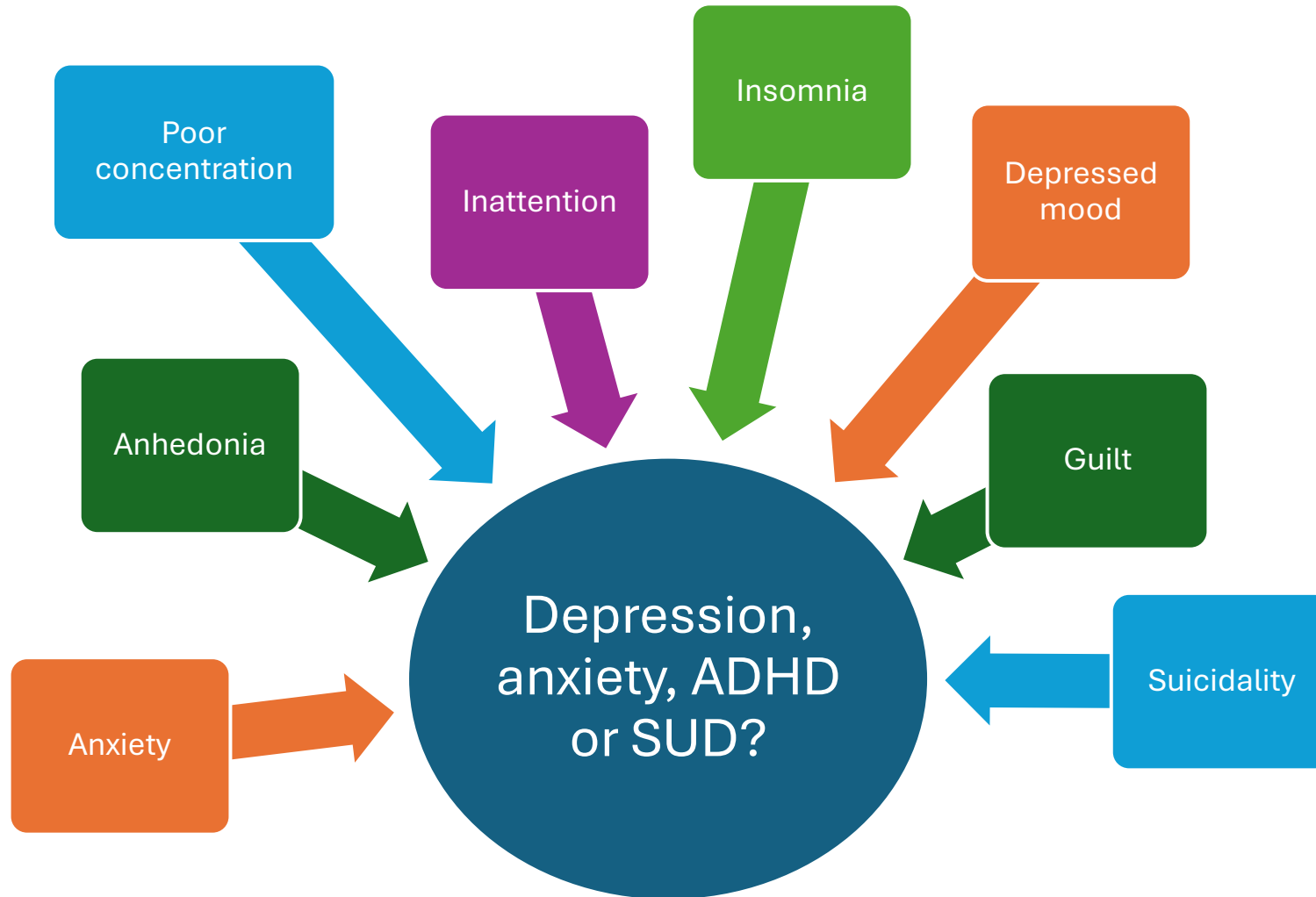
Conclusion: Stress, cravings, and negative mood are increasing prior to use events

Neurobiologically informed approach to SUD treatment



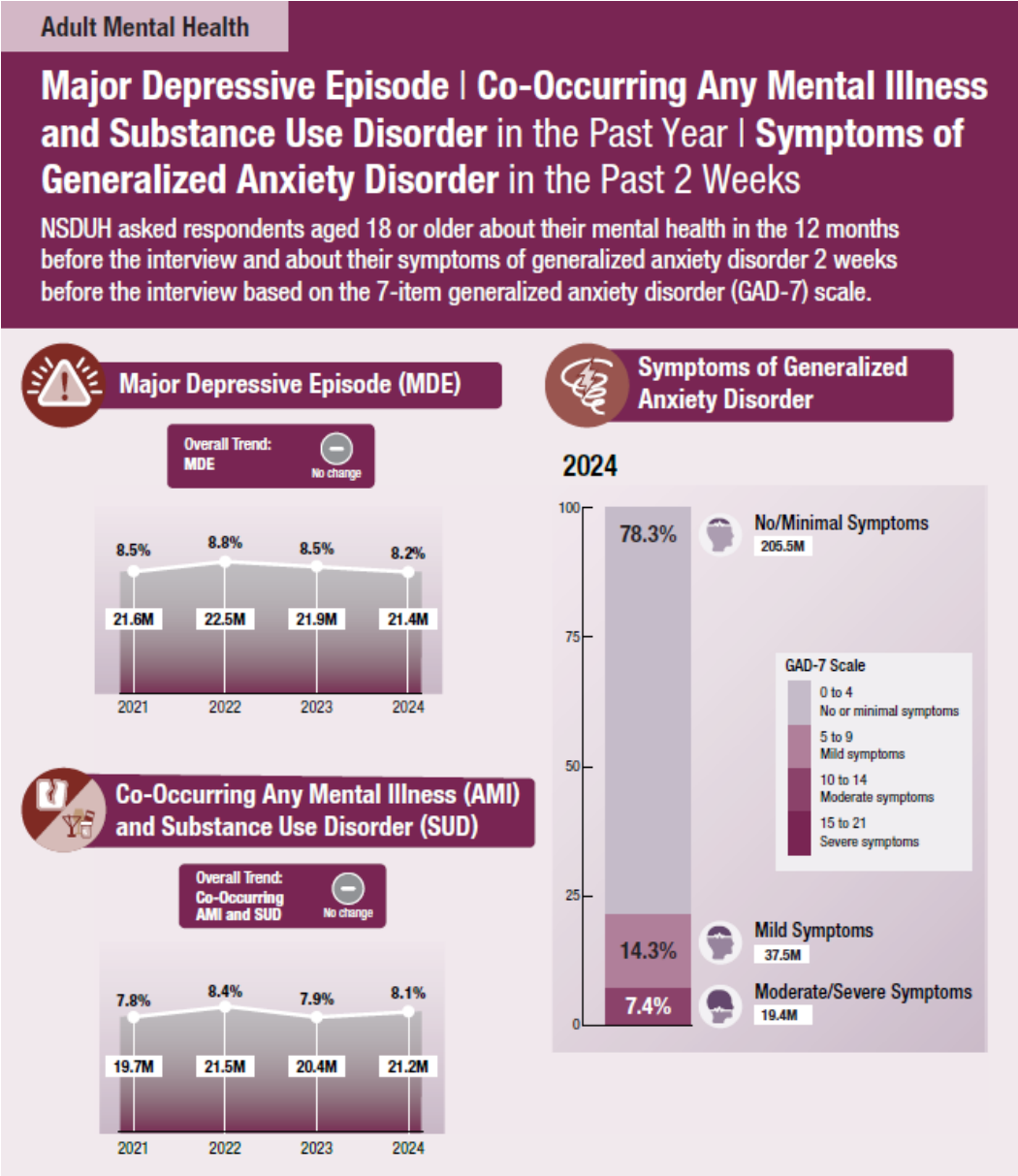
Neuropsychiatric manifestations of addiction:

Psychiatric symptoms

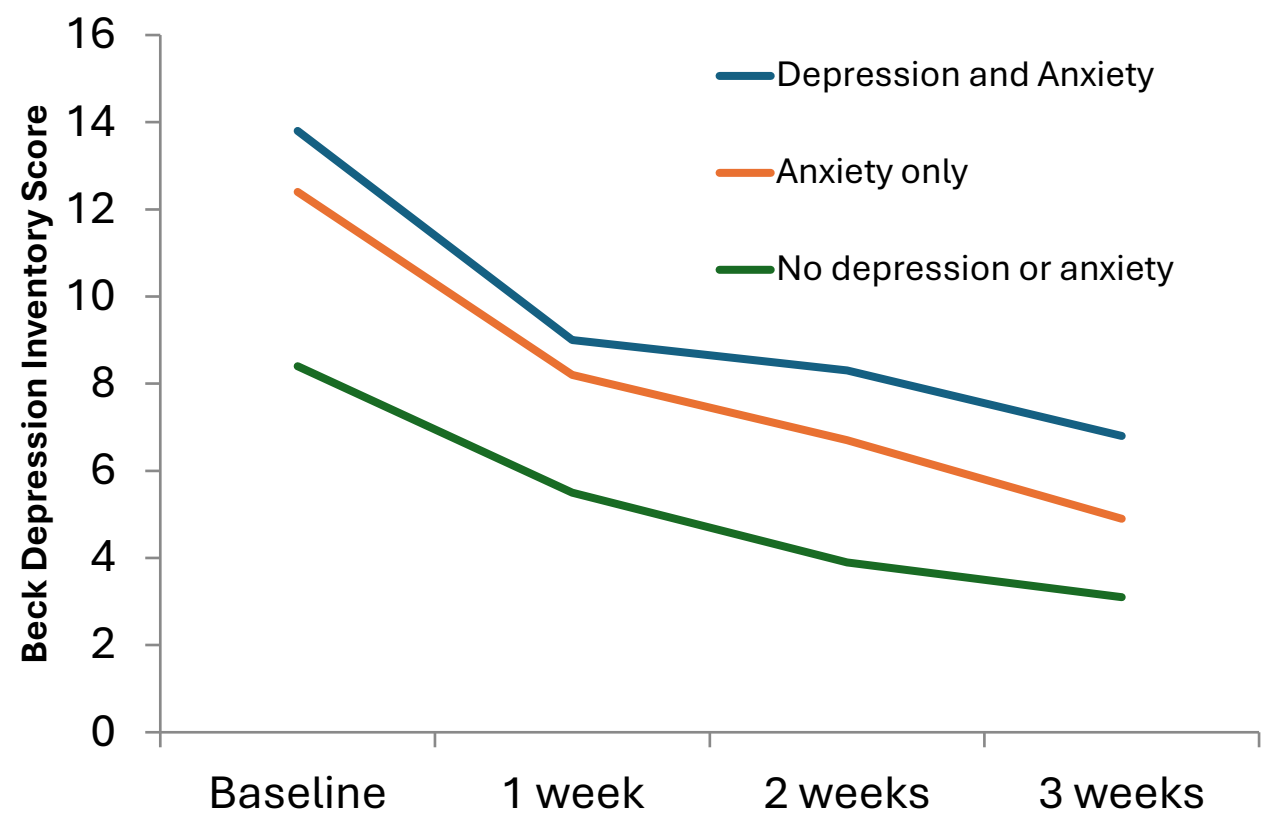


Neuropsychiatric manifestations of addiction:

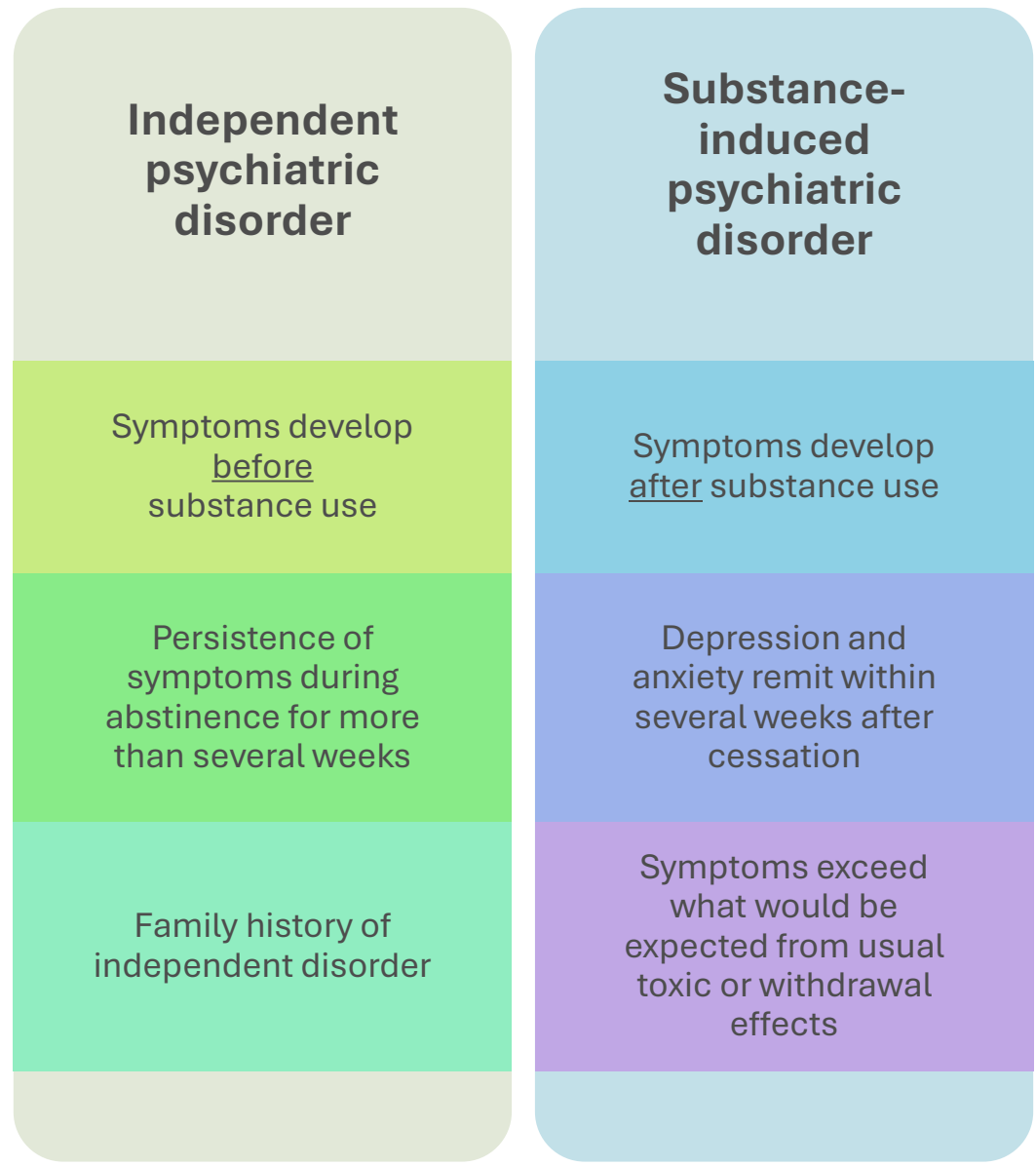
Depression



Neuropsychiatric manifestations of addiction: Primary or Secondary?



Driessen et al 2001

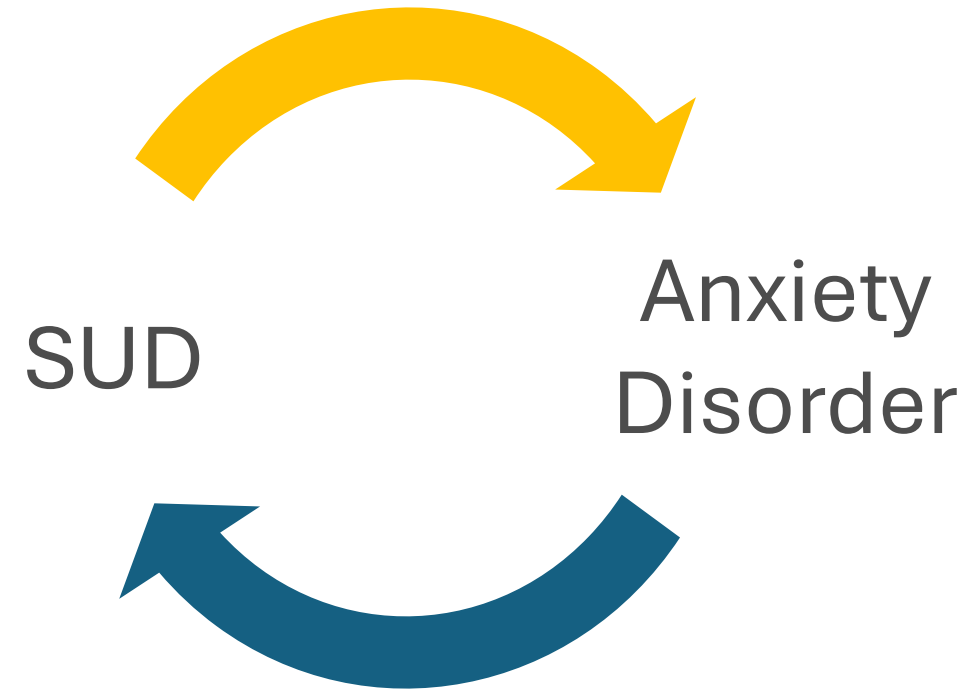


Neuropsychiatric manifestations of addiction:

Anxiety?

Anxiety Disorder	Alcohol Dependence (Odds Ratio)	Drug Dependence (Odds Ratio)
Specific phobia	2.7	3.8
Social phobia	2.7	4.5
Generalized anxiety disorder (GAD)	2.8	9.5
Panic with agoraphobia	3.5	9.2
Any anxiety disorder	3.0	6.0

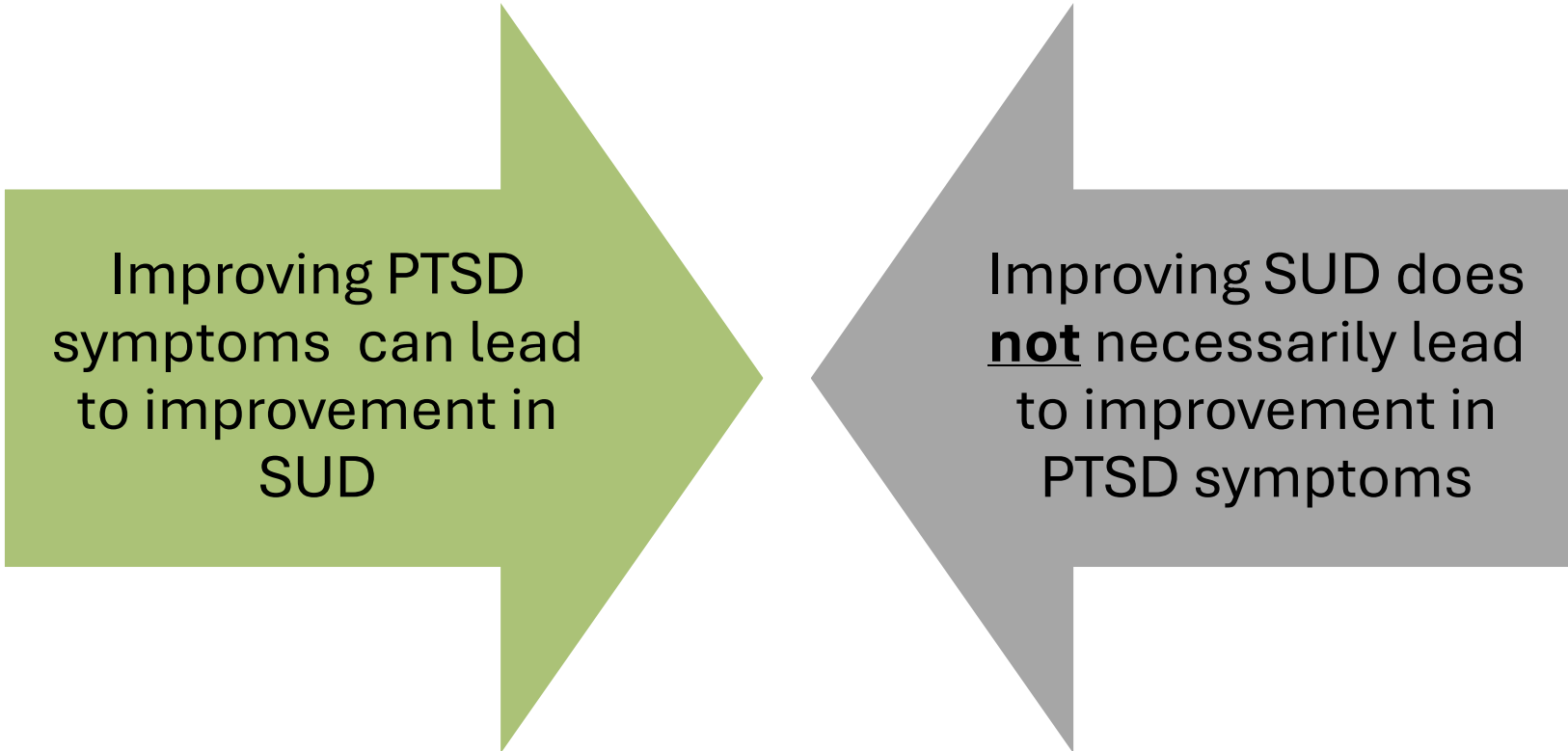
Anxiety disorders precede the development of SUD in 75% of the cases, and they both help to maintain each other



Neuropsychiatric manifestations of addiction:

Trauma symptoms

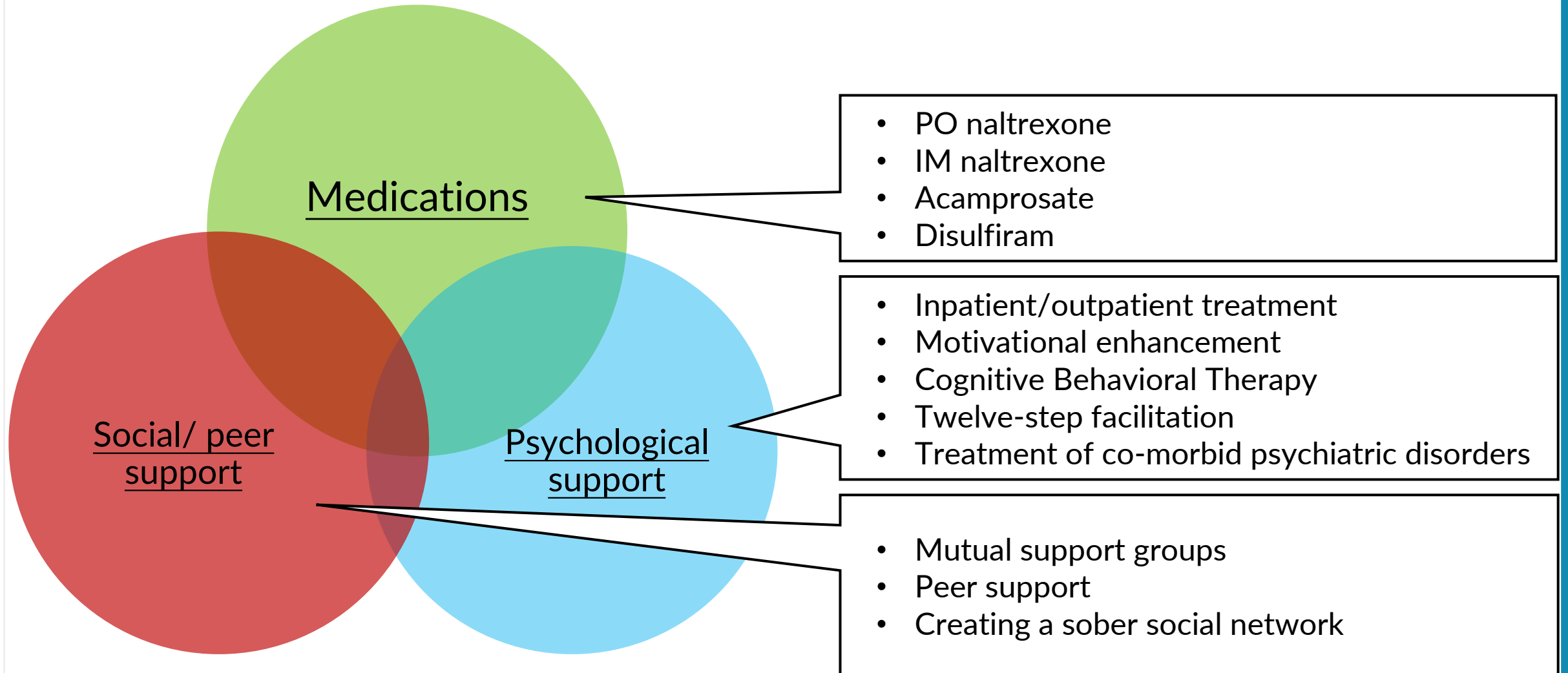
Treatment of PTSD can lead to improved SUD outcomes, but not the other way around



Improving PTSD symptoms can lead to improvement in SUD

Improving SUD does **not** necessarily lead to improvement in PTSD symptoms

Approach to treating AUD: Bio-psycho-social approach



Medications for alcohol: Initiation considerations

Naltrexone PO

Initiate at 50mg daily, can consider higher doses if indicated

AE: dizziness, somnolence, GI, fatigue. **Effects on mood controversial.**

Contraindications:
opioids,
decompensated liver cirrhosis (Child Pugh C)

Naltrexone IM

Ideally prior PO trial, but not absolute

AE: Liver toxicity even less likely due to avoidance of first-pass effect; injection site reaction

Acamprosate

666mg TID but dosing flexible (i.e. 999mg BID)

No major psychiatric interactions

AE: GI distress. Contraindicated in renal impairment (CrCl<30)

Disulfiram

Limited to those with higher motivation for abstinence

Caution in those with psychotic disorder (dopamine-beta hydroxylase)

AE: liver toxicity, psychiatric AE at higher doses, GI distress, fatigue, (Child Pugh B/C)

Medications for opioids: Initiation considerations

Buprenorphine

Target dose 24mg daily

Weekly and monthly injections
now available

Fentanyl has complicated
inductions

**No psychiatric
contraindications**

Methadone

Recent loosening of regulations
with higher starting dose and
more rapidly obtain take-home
doses

Caution:

QTc prolongation

Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs

Nora D. Volkow, M.D., Carlos Blanco, M.D., Ph.D.

Research Gap

Goal



Repurposing of medications
(e.g. glucagon-like peptide agonists)

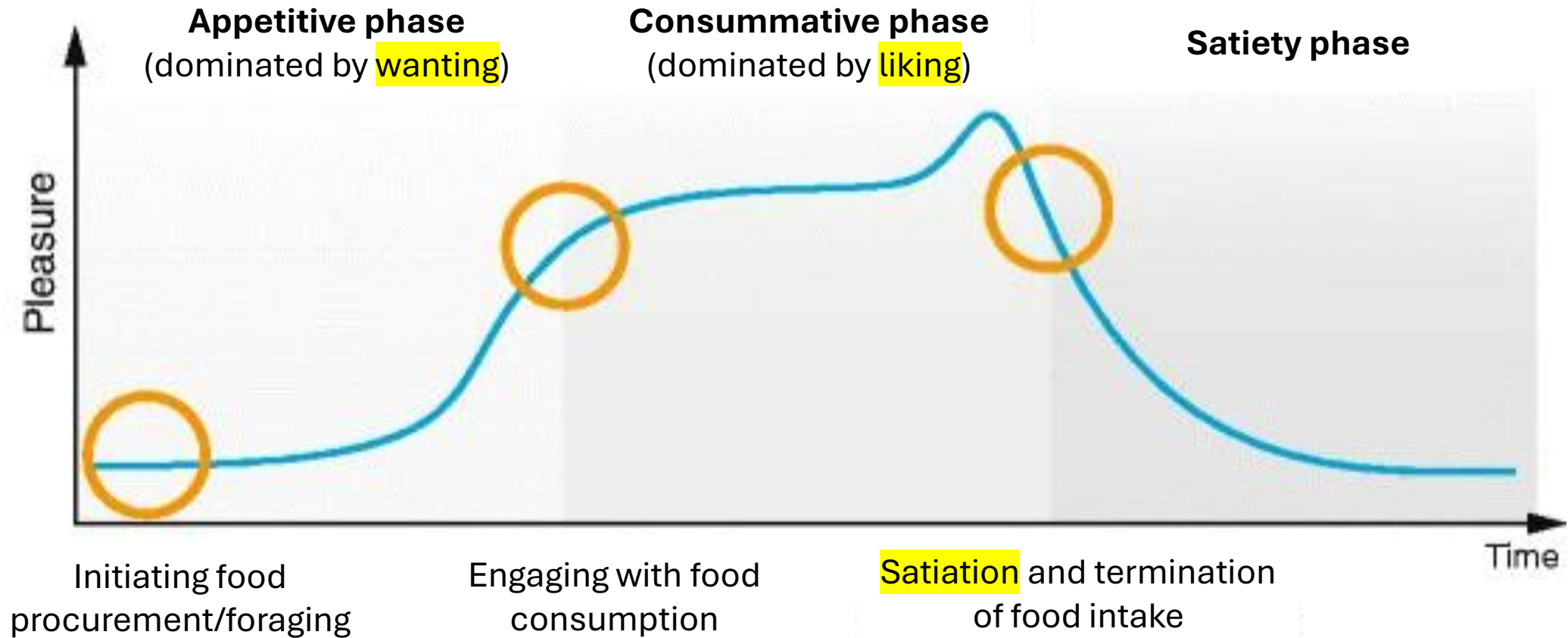
Accelerate availability
of treatment options

Research on psychedelics, such as
psilocybin, ketamine, ibogaine

Expand treatment
options for OUD

GLP-1 receptor agonists

GLP-1RAs seem to affect all phases of the “pleasure cycle”



Empirical evidence in support of GLP-1s in addressing substance use

REVIEW

The Efficacy of GLP-1 Agonists in Treating Substance Use Disorder in Patients: A Scoping Review

Mary R. Shen, MD, MS, Kwadwo Owusu-Boaitey, MD, PhD, Laura M. Holsen, PhD, and Joji Suzuki, MD

Design:

- Scoping review of the scientific literature on GLP-1s for treating substance use disorders.
- Inclusion of any manuscripts reporting the use of GLP-1s in treating SUD in humans. Excluded case report or case series.
- Extracted the following:
 - Study population
 - Study design
 - Intervention
 - Outcomes

Results: Four RCTs in humans, mixed results

Study	Population	Design	Intervention	Outcome
Angarita 2021	Cocaine n=13	Single dose; DBPC RCT cross-over	Exenatide SC 5µg vs placebo	No difference in cravings
Yammine 2021	Tobacco n=84	DBPC RCT; 6 weeks;	Exenatide ER 2mg qwk vs placebo; all received NRT and counseling	↑ abstinence with exenatide compared to placebo
Klausen 2022	Alcohol n=127	DBPC RCT; 26 weeks	Exenatide 2mg qwk vs placebo; all received counseling	No difference in drinking, but reduction in cravings; ↓ drinking for those BMI>30
Lengfeld 2023	Tobacco n=255	DBPC RCT; 12 weeks	Dulaglutide 2.gm qwk; all received varenicline and counseling	No difference in smoking

Conclusions:

- GLP1s might benefit substance use, but only if overweight?
- Further research warranted

Positive results for semaglutide for AUD

JAMA Psychiatry | [Original Investigation](#)

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder A Randomized Clinical Trial

Christian S. Hendershot, PhD; Michael P. Bremmer, MA; Michael B. Paladino, BS; Georgios Kostantinis, BA; Thomas A. Gilmore, BA; Neil R. Sullivan, BA; Amanda C. Tow, MD, PhD; Sarah S. Dermody, PhD, CPsych; Mark A. Prince, PhD; Robyn Jordan, MD, PhD; Sherry A. McKee, PhD; Paul J. Fletcher, PhD; Eric D. Claus, PhD; Klara R. Klein, MD, PhD

Design:

- Phase 2, double-blind, placebo-controlled, randomized trial of non-treatment seeking individuals with AUD to receive semaglutide weekly or placebo for 9 weeks.
- Flexible dosing but planned for 0.25mg x 4 weeks, then 0.5mg x 4 weeks, then 1.0mg x 1 week.

Primary outcomes:

- Alcohol consumption in a laboratory self-administration paradigm

Secondary outcomes:

- Alcohol consumption
- Cravings

Self-administration procedures

- Participants were presented with their preferred beverage and brand and could elect to delay drinking for up to 50 minutes for monetary reinforcement.
- Thereafter, participants were instructed to consume at their preferred pace to achieve preferred effects over 120 minutes.



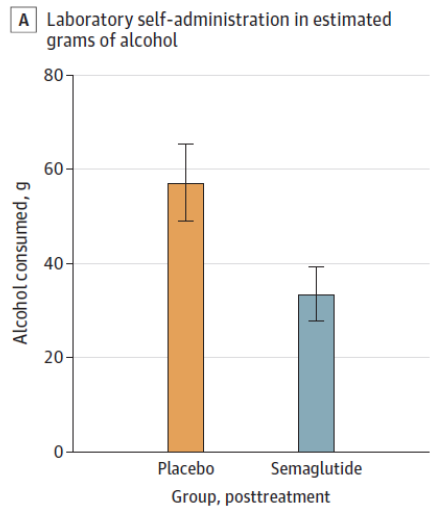
Hendershot et al JAMA Psychiatry 2025

Positive results for semaglutide for AUD

Results:

- Significant reduction in laboratory self-administration task

Figure 2. Laboratory Self-Administration

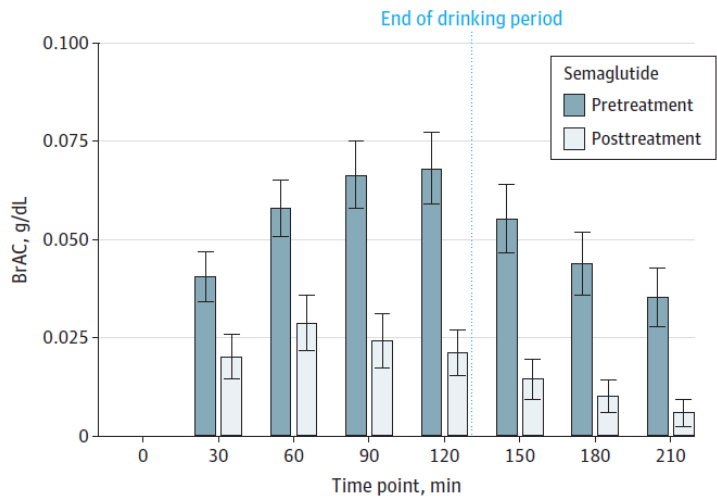
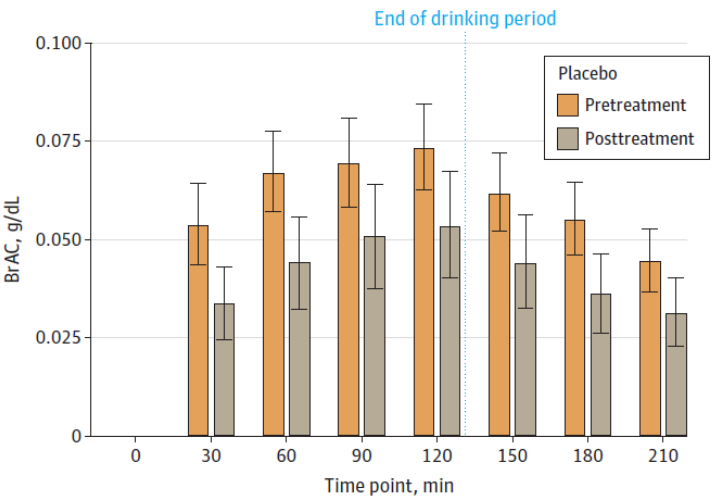


Alcohol consumed during the test, post-treatment

Placebo

Semaglutide

D Descriptive BrAC measurements during self-administration as a function of treatment condition and time point



Positive results for semaglutide for AUD in second RCT

Results:

- Overall, **significant reduction in HDD** compared to placebo, and reduced **drinks per drinking day and alcohol cravings**

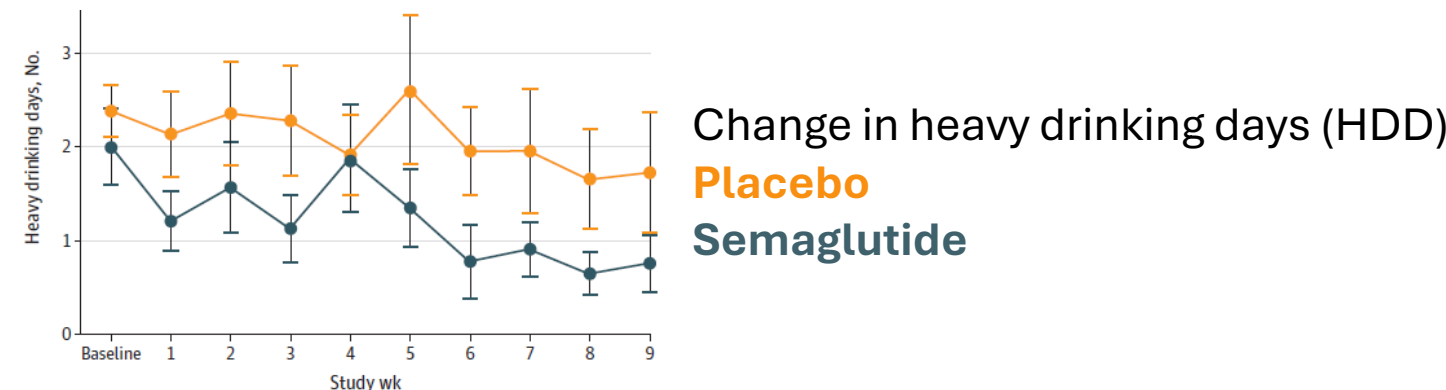
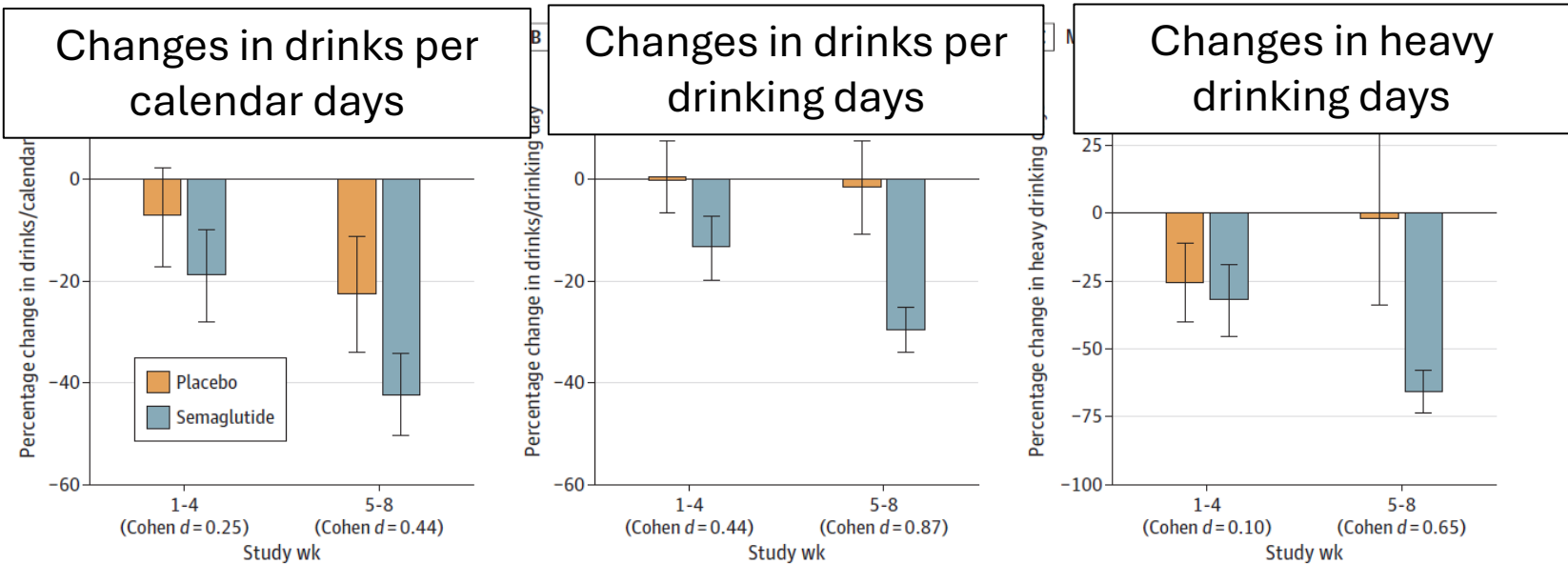


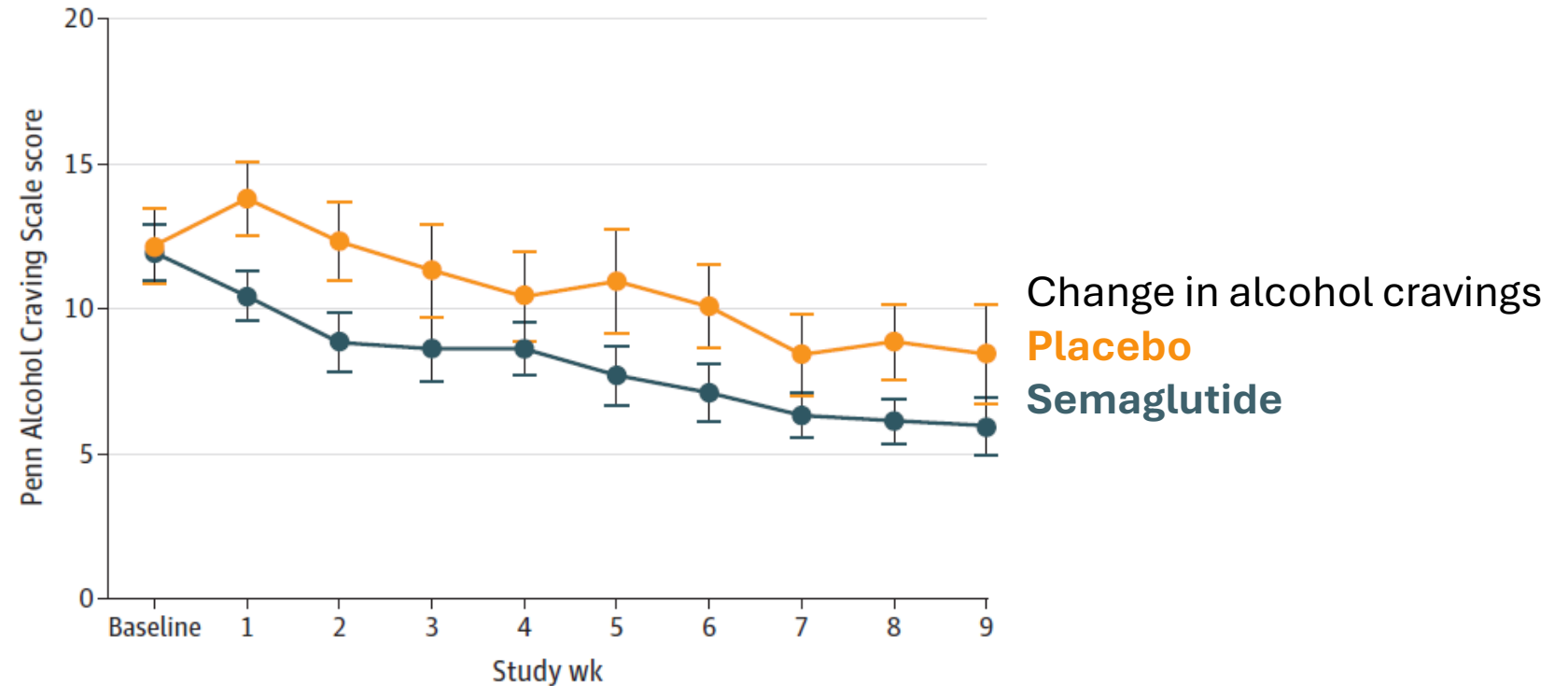
Figure 4. Medication Group Differences in Weekly Drinking and Craving as a Function of Treatment Period



Positive results for semaglutide for AUD in second RCT

Results:

- Overall, **significant reduction in HDD** compared to placebo, but reduced **drinks per drinking day and alcohol cravings**



Second RCT of semaglutide for AUD... first to enroll treatment seekers

Once-weekly semaglutide versus placebo in patients with alcohol use disorder and comorbid obesity: a randomised, double-blind, placebo-controlled trial

Mette Kruse Klausen, Signe Keller Justesen, Julie Niemann Pedersen, Line Rasmussen, Andreas Jensen, Mathias Ebbesen Jensen, Ulla B Knorr, Marianne Lerbæk Bergmann, Jens Juul Holst, Bolette Hartmann, George F Koob, Helene Benveniste, Nora D Volkow, Claus Thorn Ekstrøm, Gitte Moos Knudsen, Tina Vilsbøll, Anders Fink-Jensen

Design:

- Double-blind, placebo-controlled, randomized trial of treatment seeking individuals with AUD to receive semaglutide weekly or placebo.

Participants:

- Adults 18-70 with DSM5 moderate to severe AUD
- Co-morbid obesity (BMI>30)
- Minimum 6 heavy drinking days in prior 30 days
- Key exclusions: Severe psychiatric illness, other SUD (except tobacco), diabetes, current use of MAUDs

Intervention:

- Once weekly semaglutide SC starting at 0.25mg, escalate every 4 weeks, maximum 2.4mg (0.25 → 0.5 → 1.0 → 1.7 → 2.4)
- Up to 10 weekly standard cognitive behavioral therapy

Primary outcomes:

- Change in heavy drinking days at 26 weeks

Secondary outcomes:

- Alcohol use (drinks per drinking days, abstinence)
- Alcohol cravings, WHO risk level
- Alcohol biomarkers (i.e. PEth, LFTs)
- Metabolic (i.e. HbA1c, BMI, BP, WHO)

Second RCT of semaglutide for AUD... first to enroll treatment seekers

	Placebo (n=54)	Semaglutide (n=54)
Sex assigned at birth*		
Male	28 (52%)	27 (50.0)
Female	26 (48%)	27 (50.0)
Age		
Mean age, years	51.7 (9.8)	52.8 (9.8)
40 years and younger*	6 (11%)	5 (9%)
Older than 40 years*	48 (89%)	49 (91%)
Cohabiting or married	29 (54%)	22 (41%)
Race or ethnicity		
Asian	0	4 (7%)
Black or African American	1 (2%)	1 (2%)
White	53 (98%)	49 (91%)
Employed	40 (74%)	39 (72%)
Education		
Lower secondary school	3 (6%)	3 (6%)
Upper secondary school	2 (4%)	2 (4%)
Vocational education or short-cycle higher education	21 (39%)	14 (26%)
Medium-cycle higher education or higher education	28 (52%)	35 (65%)
Previous treatment with a glucagon-like peptide-1	8 (15%)	5 (9%)

	Placebo (n=54)	Semaglutide (n=54)
Previous pharmacological treatment for alcohol use disorder		
Disulfiram	9 (17%)	10 (19%)
Acamprosate	5 (9%)	5 (9%)
Naltrexone	1 (2%)	1 (2%)
Nalmefene	0	0
Alcohol use disorders identification score†		
Alcohol use disorders identification consumption score‡		
ICD-10: alcohol dependence		
3 symptoms	5 (9%)	3 (4%)
4 symptoms		
5 symptoms		
6 symptoms		
Diagnostic and Statistical Manual alcohol use disorder		
Mild (2–3 symptoms)	0	0
Moderate (4–5 symptoms)	11 (21%)	5 (9%)
Severe (>5 symptoms)	43 (80%)	49 (91%)

(Table 1 continues in next column)

Approximately 5 drinks per day

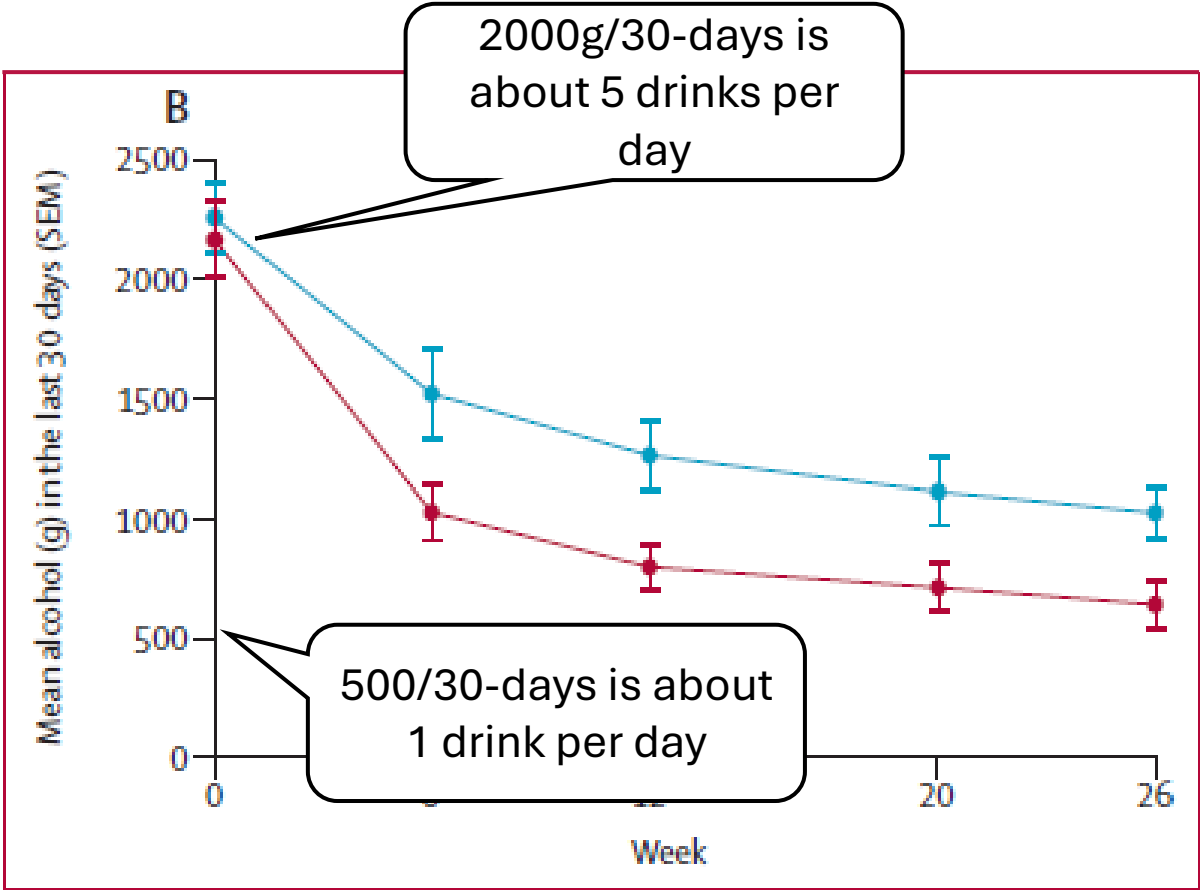
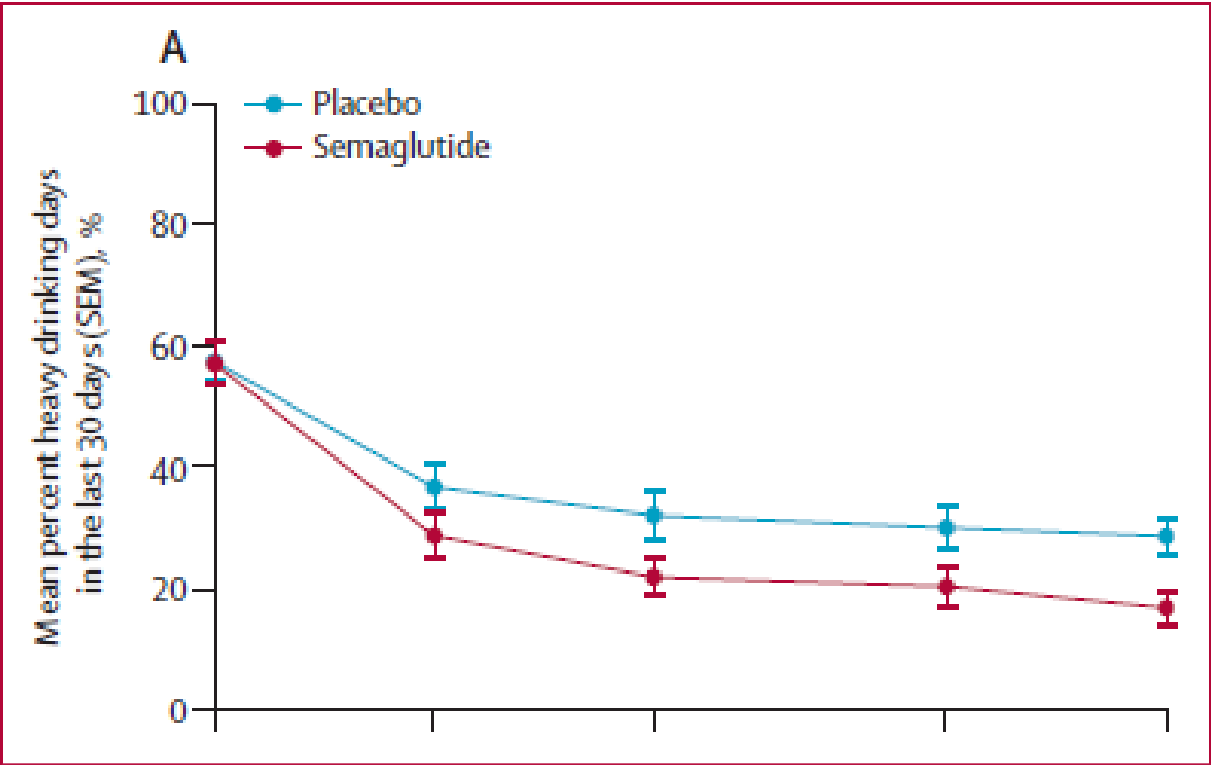
Approximately 300-500ng/ml PEth

	Placebo (n=54)	Semaglutide (n=54)
(Continued from previous column)		
Heavy drinking days§	17.2 (7.4)	17.1 (8.2)
Heavy drinking days randomisation start		
6–11 days*	15 (28%)	17 (32%)
12–17 days*	14 (26%)	14 (26%)
18–23 days*	10 (19%)	7 (13%)
24–30 days*	15 (28%)	16 (30%)
Days without alcohol consumption	8.5 (7.3)	9.1 (7.5)
Total alcohol consumption, g of alcohol per 30 days§	2246.6 (1091.9)	2155.3 (1171.5)
Phosphatidyl ethanol, µmol/L	0.7 (0.6)	0.5 (0.5)
WHO risk drinking level¶		
Low	1 (1.9%)	1 (1.9%)
Medium	12 (22.6%)	16 (29.6%)
High	23 (42.6%)	19 (35.2%)
Very high	18 (33.3%)	18 (33.3%)
Fagerströms test for Nicotine Dependence score	4.2 (2.8)	3.5 (2.5)
Cigarettes per day	14.9 (10.1)	13.2 (9.5)
Bodyweight, kg	105.2 (15.5)	100.3 (12.0)
BMI, kg/m²	35.2 (4.4)	33.7 (3.3)
Glycated haemoglobin**	5.4 (0.4)	5.5 (0.3)

Second RCT of semaglutide for AUD... first to enroll treatment seekers

	Placebo (n=54)	Semaglutide (n=54)	Estimated treatment difference, placebo vs semaglutide (95% CI)	p value
Self-reported drinking and alcohol scales				
Heavy drinking days, percentage points (primary endpoint)*	-26.4 (-34.1 to -18.6)	-41.1 (-48.7 to -33.5)	-13.7 (-22.0 to -5.4)	0.0015
Total alcohol consumption, g/30 days*	-1025.9 (-1260.0 to -791.1)	-1550.2 (-1868.2 to -1232.1)	-467.5 (-739.5 to -195.4)	<0.0009
Days without alcohol consumption, percentage points*	27.6 (19.8-35.5)	38.9 (30.6-47.3)	10.1 (-0.0 to 20.2)	0.051
Change in drinks per drinking day*	-2.1 (-3.1 to -1.1)	-3.5 (-4.5 to -2.6)	-1.5 (-2.6 to -0.5)	0.0051
Reduction in WHO risk drinking level†	-1.24 (-1.54 to -0.94)	-1.75 (-2.04 to -1.45)	-0.52 (-0.89 to -0.16)	0.0055
Alcohol craving (Penn alcohol craving scale score)‡	-6.1 (-7.6 to -4.6)	-9.2 (-10.8 to -7.6)	-3.1 (-5.1 to -1.2)	0.0020
Alcohol use disorders identification test score§	-6.3 (-7.8 to -4.7)	-9.9 (-11.6 to -8.2)	-3.3 (-5.5 to -1.1)	0.0044
Alcohol use disorders identification test consumption score¶	-2.7 (-3.4 to -1.9)	-4.2 (-5.0 to -3.5)	-1.5 (-2.6 to -0.4)	0.0071
Alcohol biomarkers				
Phosphatidyl ethanol, µmol/L	0.00 (-0.10 to 0.11)	-0.24 (-0.34 to -0.13)	-0.28 (-0.41 to -0.15)	<0.0001
Liver and pancreas parameters				
Alanine aminotransferase, U/L	-6.5 (-11.0 to -2.0)	-12.5 (-21.2 to -3.9)	-3.3 (-11.0 to 4.4)	0.40
γ-glutamyl transferase, U/L	-10.2 (-17.5 to -2.9)	-36.0 (-52.2 to -19.7)	-24.2 (-33.4 to -15.1)	<0.0001
Mean corpuscular volume, fL	0.4 (-0.6 to 1.1)	-1.3 (-1.9 to -0.6)	-1.7 (-2.6 to -0.7)	0.0007
Amylase, U/L	-0.9 (-2.7 to 1.0)	4.7 (2.8 to 6.6)	5.1 (2.5 to 7.7)	0.0002
FIB-4	0.0 (-0.1 to 0.1)	-1.1 (-3.2 to 1.0)	0.0 (-0.1 to 0.2)	0.67

Second RCT of semaglutide for AUD... first to enroll treatment seekers



Effects of once-weekly semaglutide compared to placebo on reduction in heavy drinking and total alcohol consumption

Third RCT of semaglutide for AUD using the oral formulation

Oral Semaglutide for Alcohol Use Disorder: A Randomized Clinical Trial

Joseph P. Schacht, Ph.D., ¹ Joseph T. Sakai, M.D.,¹ Kristen Raymond, B.A.,¹ Robert Shelton, M.S.¹

Design:

- Double-blind, placebo-controlled, randomized trial of treatment seeking individuals with AUD to receive oral semaglutide weekly or placebo.

Participants:

- Adults with DSM5 moderate to severe AUD
- BMI ≥ 25 (randomization strata)
- Reporting ≥ 28 drinks/week for men, or ≥ 21 drinks/week for women
- Minimum 1 heavy drinking days in prior week ($\geq 5/\geq 4$ drinks/d for men/women)
- Key exclusions: current psychiatric disorders, current other mode/sev SUD (except urine+ for cannabis), past month use of MAUDs, any prior GLP-1 use, current use of psychotropic meds except antidepressants

Intervention:

- Once daily semaglutide PO 3mg x 4 weeks $\rightarrow$ 7mg x 4 weeks
- Up to 10 weekly standard cognitive behavioral therapy

Primary outcomes:

- Alcohol cue-reactivity at 6 weeks using VAS

Secondary outcomes:

- Average alcohol use during weeks 5-8
- Drinks per calendar day
- Heavy drinking days per week
- fMRI cue-reactivity task

Third RCT of semaglutide for AUD using the oral formulation

TABLE 1. Pretreatment characteristics by treatment group for all randomized participants^a

Characteristic	Placebo (N=26)		Semaglutide (N=24)		Total (N=50)	
	N	%	N	%	N	%
Sex						
Female	13	50	15	63	28	56
Male	13	50	9	37	22	44
Race						
American Indian or Alaska Native	1	4	0	0	1	2
Asian	1	4	1	4	2	4
Black or African American	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	24	92	23	96	47	94
Hispanic ethnicity	0	0	1	4	1	2
WHO risk drinking level						
Medium	0	0	1	4	1	2
High	12	46	8	33	20	40
Very High	14	54	15	63	29	58
Abstinent drinking goal	3	12	4	17	7	14
Cigarette smoker	3	12	4	17	7	14
Cannabis user (past year)	7	27	10	42	17	34
	Mean	SD	Mean	SD	Mean	SD
Age (years)	53.5	10.4	48.6	9.6	51.1	10.2
DSM-5 AUD criteria	6.6	2.1	7.7	2.0	7.1	2.1
Alcohol consumption						
Drinks per calendar day	6.6	3.0	6.3	2.6	6.4	2.8
Drinks per drinking day	7.3	3.3	8.0	2.9	7.6	3.1
Drinking days per week	6.4	0.9	5.7	1.6	6.1	1.3
Heavy drinking days per week	5.4	1.6	4.5	1.9	5.0	1.8
Body mass index	32.1	5.1	30.7	3.9	31.4	4.6
Liver function tests (U/L)						
Aspartate aminotransferase	24.7	9.6	25.6	11.2	25.1	10.3
Alanine aminotransferase	26.6	13.1	27.3	19.6	26.9	16.4

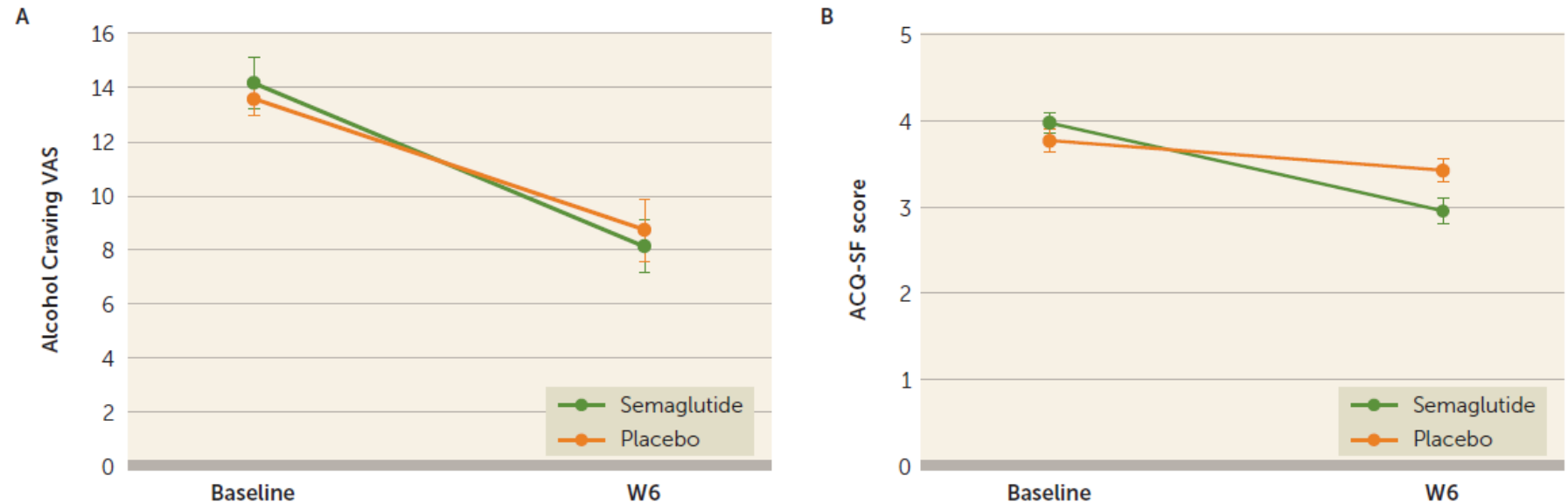
^a AUD, alcohol use disorder; WHO, World Health Organization.

Third RCT of semaglutide for AUD using the oral formulation

Results:

- Primary outcome: **No significant difference** in the score on the VAS for item 1 at week 6 between semaglutide and placebo (Fig A).
- But ACQ-SF scores were significantly lower (Fig B).

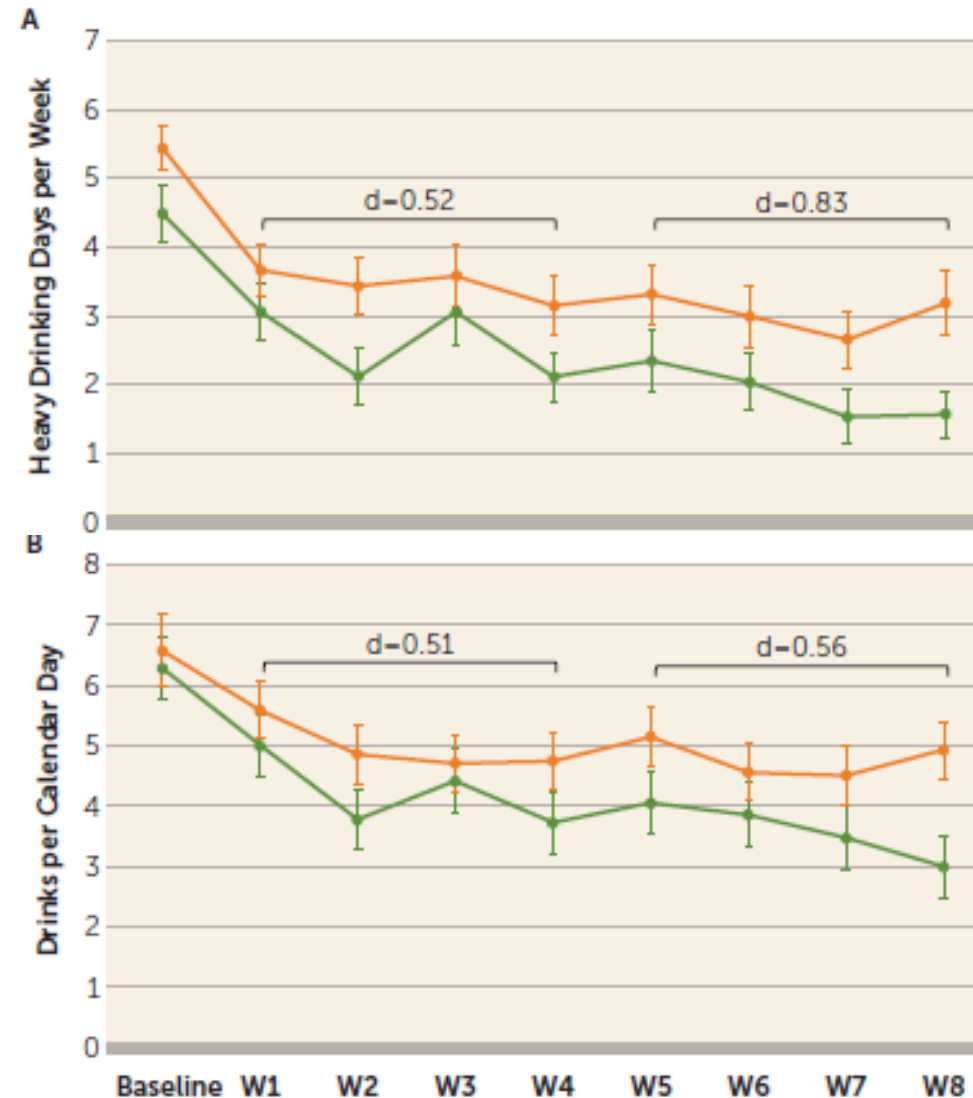
FIGURE 2. Alcohol cue-elicited craving at baseline and week 6 by treatment group^a



Third RCT of semaglutide for AUD using the oral formulation

Results:

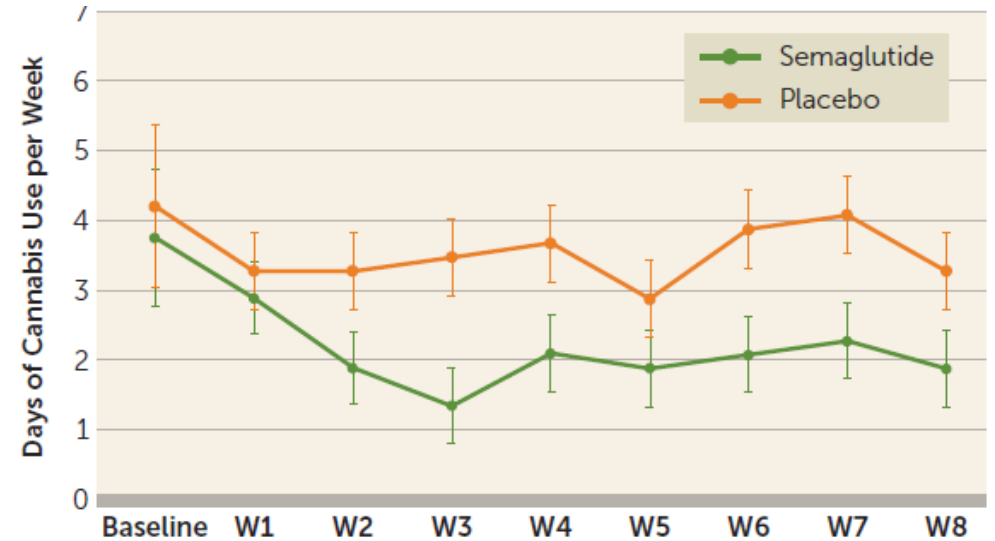
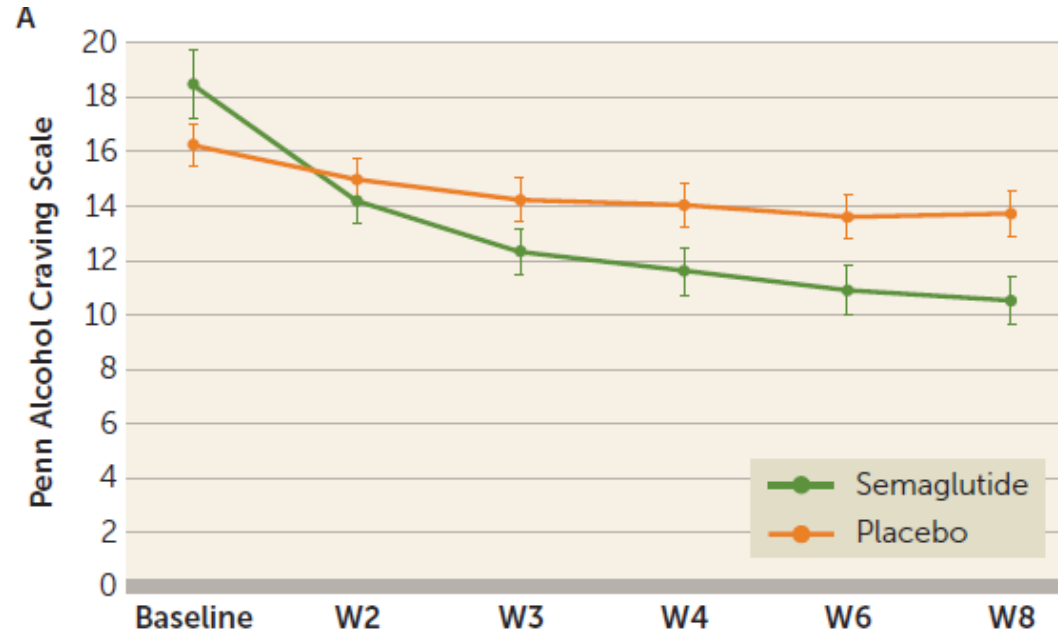
- Overall, **significant reduction in Heavy Drinking days** but not drinking days or drinks per day



Third RCT of semaglutide for AUD using the oral formulation

Results:

- Significant reduction in alcohol cravings as well as significant reduction in cannabis use



So we have 3 RCTs for semaglutide for AUD, all positive!

- Overall semaglutide well tolerated in all trials
- Adds to the growing body of evidence that GLP-1s will be effective treatments for AUD
- However, unclear generalizability due to:
 - ✓ Hendershot trial enrolled those who were NOT treatment seeking
 - ✓ Both Klausen and Schacht trials enrolled those with obesity/overweight

Psychedelics

Psilocybin disrupts the default mode network (DMN)

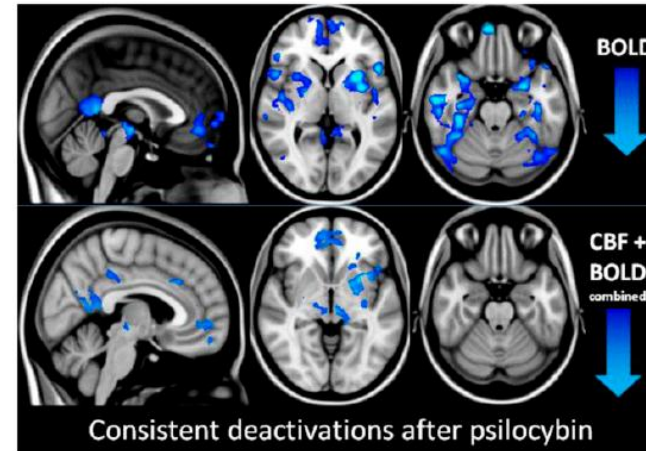
Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin

Robin L. Carhart-Harris^{a,b}, David Erritzoe^{a,c}, Tim Williams^b, James M. Stone^a, Laurence J. Reed^a, Alessandro Colasanti^a, Robin J. Tyacke^a, Robert Leech^d, Andrea L. Malizia^b, Kevin Murphy^e, Peter Hobden^e, John Evans^e, Amanda Feilding^f, Richard G. Wise^e, and David J. Nutt^{a,b,1}

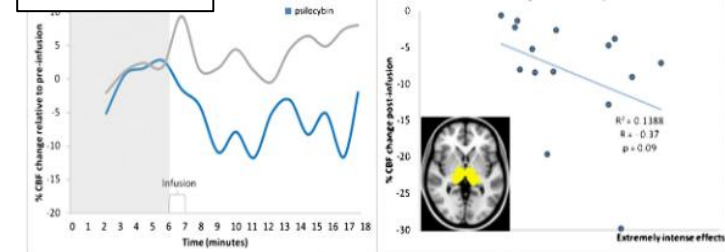
^aNeuropsychopharmacology Unit, ^bImperial College London, London W12 0NN, United Kingdom; ^cAcademic Unit of Psychiatry, University of Bristol, Bristol BS8 2BN, United Kingdom; ^dBrain Research Imaging Centre, Cardiff University, Cardiff CF10 3AT, United Kingdom; ^eThe Beckley Foundation, Beckley Park, Oxford OX3 9SY, United Kingdom; and ^fNeurobiology Research Unit, Rigshospitalet, and Center for Integrated Molecular Brain Imaging, University of Copenhagen, DK-2100 Copenhagen, Denmark



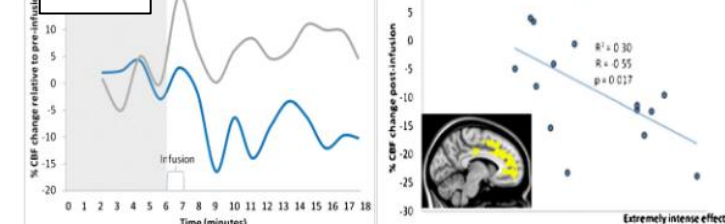
- 15 healthy volunteers (5F/10M) scanned during psilocybin IV infusion (2mg over 60s)
- ASL and BOLD fMRI
- Results:**
 - NO increase in CBF/BOLD
 - Only decrease noted, maximal in hub regions such as thalamus, ACC, mPFC, PCC
 - Decreased coupling between mPFC and PCC
 - Magnitude of decrease correlated with intensity of the subjective effects



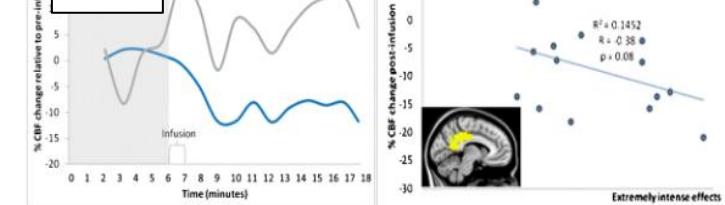
Thalamus



ACC

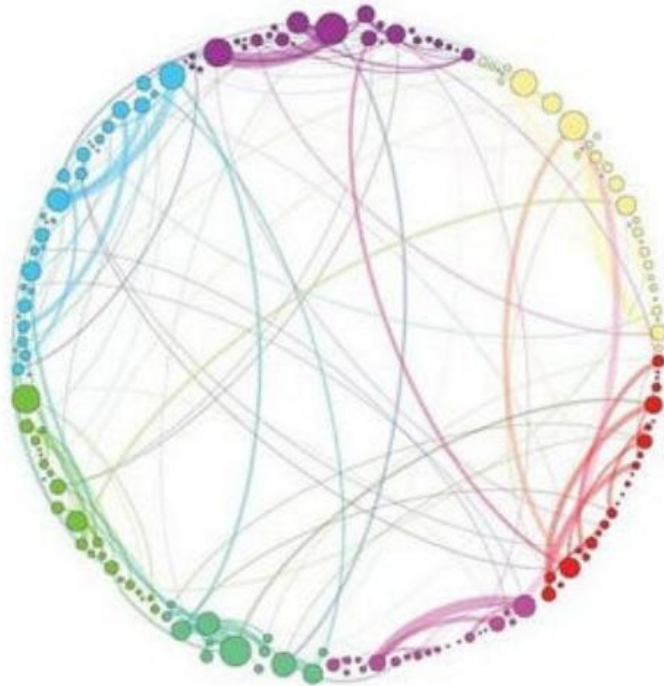


PCC

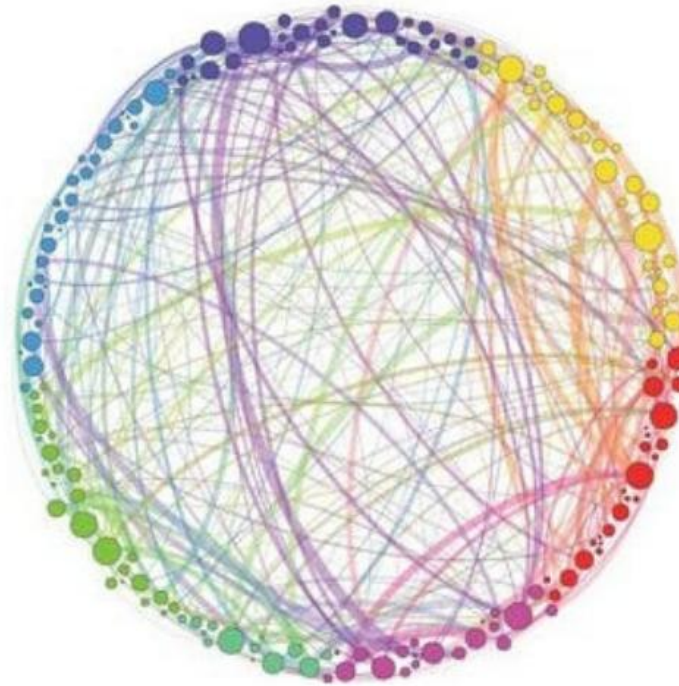


Psychedelics help to increase neuroplasticity

Placebo



Psilocybin



Preparation and integration therapies likely to be important in establishing the “set and setting” and minimizing adverse effects

Preparation

- Develop rapport
- Set expectations
- Safety protocols
- Goals and intentions

Administration

- Single or multiple dosing
- Therapist present in-person
- Eye shades and headphones
- Non-directive support

Integration

- Making sense of the experience
- Incorporate insight into normal day to day



Psilocybin led to greater abstinence vs nicotine patch in those who smoke cigarettes



Original Investigation | Substance Use and Addiction

Psilocybin or Nicotine Patch for Smoking Cessation A Pilot Randomized Clinical Trial

Matthew W. Johnson, PhD; Gideon P. Naudé, PhD; Peter S. Hendricks, PhD; Albert Garcia-Romeu, PhD

Objective: To compare smoking abstinence in smokers receiving psilocybin + CBT vs NRT + CBT

Methods: Open-label pilot RCT, either 1 session of psilocybin (30mg/70kg) or nicotine patch, both receiving 13 weeks of CBT...

Outcomes:

Primary: Biochemically verified prolonged abstinence at 6 months

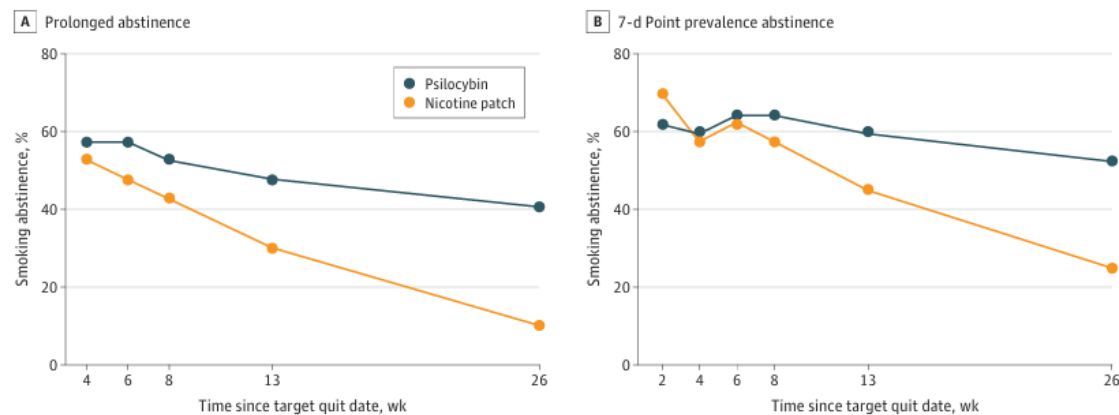
Secondary: 7-day point prevalence abstinence at 6 months

Johnson et al JAMA Network Open 2026

Results:

- A total of 82 participants, 68 completed the 6-month f/u
- Significantly more in psilocybin group with prolonged abstinence (40.5% vs 10.0%, $p=0.003$)
- Significantly more in psilocybin group with 7-day point prevalence abstinence (52.4% vs 25.0%, $p=0.01$)
- No SAEs attributed to psilocybin

Figure 3. Smoking Abstinence Rates Between the Psilocybin and Nicotine Patch Groups



Conclusion:

- Psilocybin administration led to greater smoking abstinence compared to NRT. Intervention well tolerated.

Psilocybin with greater reduction in cocaine use vs placebo in cocaine use disorder

Psilocybin in the Treatment of Cocaine Use Disorder A Randomized Clinical Trial

Peter S. Hendricks, PhD; Sara N. Lappan, PhD; Richard C. Shelton, MD; Adrienne C. Lahti, MD; Karen L. Cropsey, PsyD; Matthew W. Johnson, PhD; Melissa Bradley, MPH; Otto Simonsson, PhD; Lori L. Davis, MD; Daniel H. Grossman, MA; Cynthia E. Ortiz, PhD

Objective: To compare cocaine use in those with cocaine use disorder receiving either psilocybin vs active placebo (diphenhydramine)

Methods: Double-blind, placebo-controlled, RCT, either 1 session of psilocybin (25mg/70kg) or 100mg diphenhydramine, both receiving manualized CBT session before and after.

Outcomes:

Primary: Percentage cocaine abstinent days

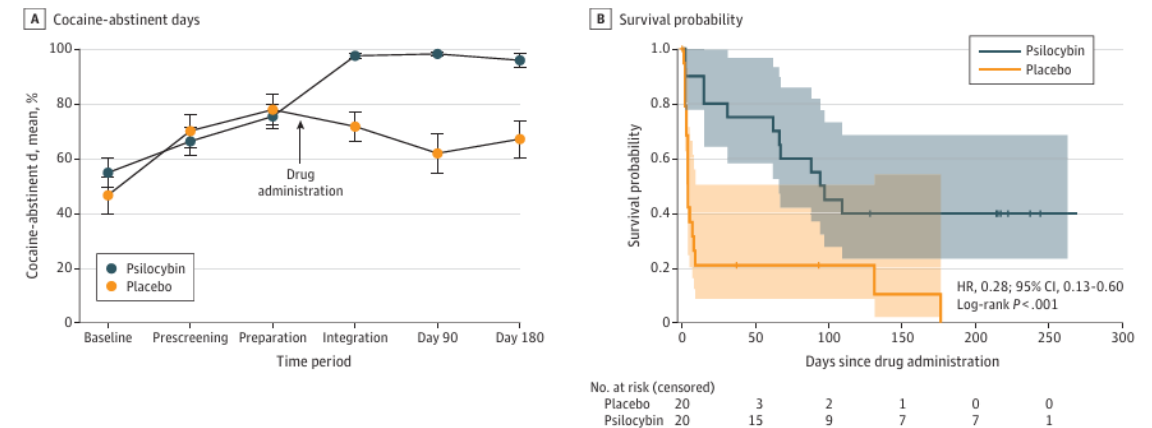
Secondary: Rates of complete abstinence, time to first relapse

Johnson et al JAMA Network Open 2026

Results:

- A total of 40 participants, 82.5% men, 82.5% black, 65% with annual income <\$20K
- Psilocybin:
 - Higher % of abstinent days ($p=0.001$)
 - Greater odds of complete abstinence (OR 18.4, $p=0.007$)
 - Reduced relapse risk (HR 0.28, $p=0.001$)
- No SAEs attributed to psilocybin; blinding was not successful

Figure 2. Line Chart Showing Percentage of Cocaine-Abstinent Days and Plot Showing Survival Probability



Conclusion:

- Psilocybin administration led to more abstinent days, and 18 times greater odds of complete abstinence compared to diphenhydramine.

Psilocybin improves drinking outcome in the first DBRCT

Research

JAMA Psychiatry | Original Investigation

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder A Randomized Clinical Trial

Michael P. Bogenschutz, MD; Stephen Ross, MD; Snehal Bhatt, MD; Tara Baron, MA; Alyssa A. Forcehimes, PhD; Eugene Laska, PhD; Sarah E. Mennenga, PhD; Kelley O'Donnell, MD, PhD; Lindsey T. Owens, MA; Samantha Podrebarac, MA; John Rotrosen, MD; J. Scott Tonigan, PhD; Lindsay Worth, MA

Design: Double-blind randomized clinical trial

Methods: 95 patients with AUD randomly assigned to receive two sessions of either psilocybin 25mg or diphenhydramine. All received 12 weeks of manualized psychotherapy.

Primary outcomes:

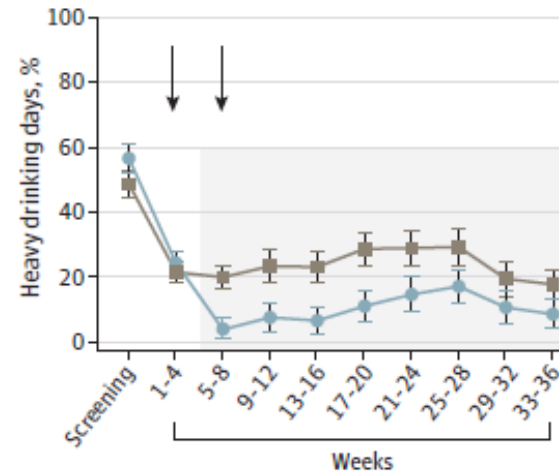
- Percent heavy drinking days (%HDD) over the 32-week follow-up
- % drinking days (%DD); Drinks/drinking days (DDD)

Bogenschutz et al JAMA 2022

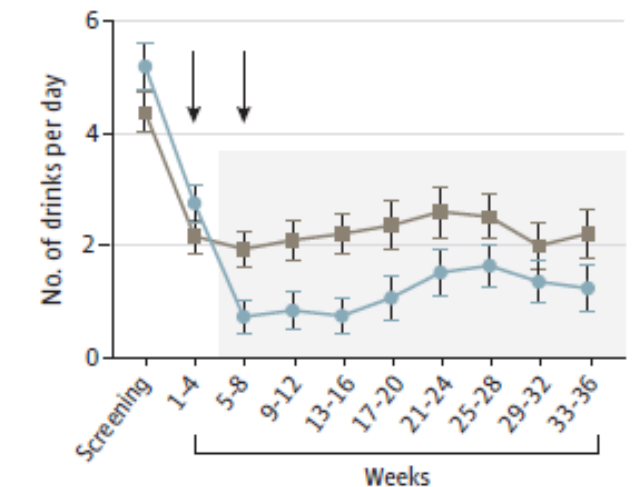
Results:

- During follow-up, **%HDD was 9.7% vs 23.6%** ($p=0.01$)
- Lower %DD and DDD in psilocybin
- No serious AEs
- Blinding NOT successful

A Percent heavy drinking days



C Drinks per day



Conclusion:

- Psilocybin compared to control led to greater reduction in drinking and heavy drinking

Psilocybin did NOT improve drinking outcomes in the second DBRCT

Psilocybin-assisted therapy for relapse prevention in alcohol use disorder: a phase 2 randomized clinical trial

Nathalie M. Rieser,^{a,*} Raoul Bitar,^a Simon Halm,^a Christina Rossgoderer,^a Ladina P. Gubser,^a Maeva Thévenaz,^a Yara Kreis,^a Robin von Rotz,^a Carlos Nordt,^a Monika Visentini,^a Flora Moujaes,^a Etna J. E. Engeli,^a Andres Ort,^a Erich Seifritz,^a Franz X. Vollenweider,^a Marcus Herdener,^{a,b} and Katrin H. Preller^{a,b}

^aDepartment of Adult Psychiatry and Psychotherapy, Psychiatric University Clinic Zurich and University of Zurich, Lengstrasse 31, Zurich 8032, Switzerland



Design: Double-blind, placebo-controlled randomized trial

Methods: 37 patients with AUD who recently completed withdrawal treatment were randomly assigned to receive one session of either psilocybin 25mg or placebo along with a 5-session manualized psychotherapy.

Primary outcomes:

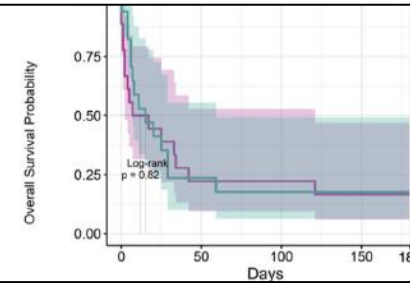
- Abstinence
- Mean alcohol use at 4 weeks in drinks per day

Rieser et al 2025

Results:

- No difference in abstinence duration (16.8 vs 13.8 days)
- No difference in mean drinks per day at 4 weeks (0.51 vs 0.48)

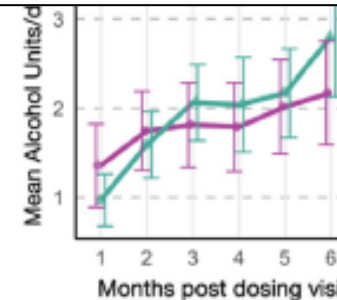
Abstinence at 6 months



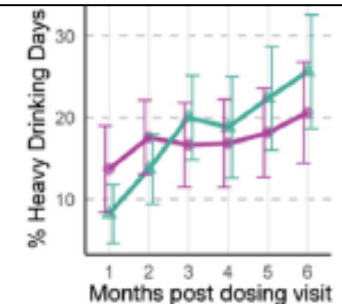
Group

- Placebo
- Psilocybin

Mean alcohol use at 6 months



% HDD at 6 months



Conclusion:

- Single-session of 25mg psilocybin with psychotherapy might not be sufficient for those with AUD recently completing inpatient treatment

Current state of evidence for psychedelics as treatments for SUD

Psychedelic	SUD	Quality of evidence
LSD	Alcohol	Fair : Methodological issues even though RCTs
	Opioid	Fair : Study of parolees, but daily urines a strength
Psilocybin	Alcohol	Mixed : <u>Two RCTs</u> with one positive and one negative results
	Tobacco	Poor : Open-label (waiting for phase 2 results; NIDA funding for phase 3)
Ketamine	Cocaine	Promising : <u>One pilot RCT</u> with promising short-term benefit
	Opioids	Fair : 3 RCTs but not as adjunct to MOUD and questionable methods; may be useful for opioid withdrawal especially precipitated withdrawal
	Alcohol	Promising : <u>Two pilot RCTs</u> , three uncontrolled studies, too early to tell
	Cannabis	Poor : One open-label study
	Benzos	Poor : On open-label study
Ibogaine	Opioid	Poor : Uncontrolled studies only; cardiac arrhythmias
MDMA	Alcohol	Poor : One open-label study

Conclusions

- Addiction remains a major public health issue in the US
- Addiction is best understood as a chronic brain illness that benefits a biopsychosocial approach to treatment
- Neuropsychiatric manifestations are common in SUD
- New novel treatments are emerging, possibly challenging existing neurobiologic understanding of addiction treatment



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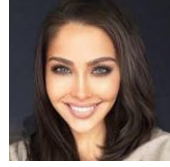
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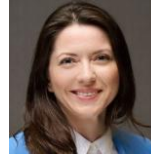
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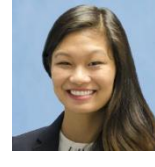
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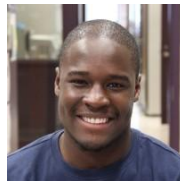


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