

GLP-1s and Management of Substance Use Disorders

September 19, 2026

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Disclosures

- I receive research funding to conduct clinical trials including for semaglutide for OUD funded by NIDA (R21DA060304) and Brenipatide for OUD funded by Eli Lilly, both are ongoing.
- I received in-kind support from Braeburn to use Brixadi to conduct a NIH-funded trial (R21DA060411) which ended August 2026.
- I have no other relevant financial conflicts of interest to disclose.



Learning Objectives

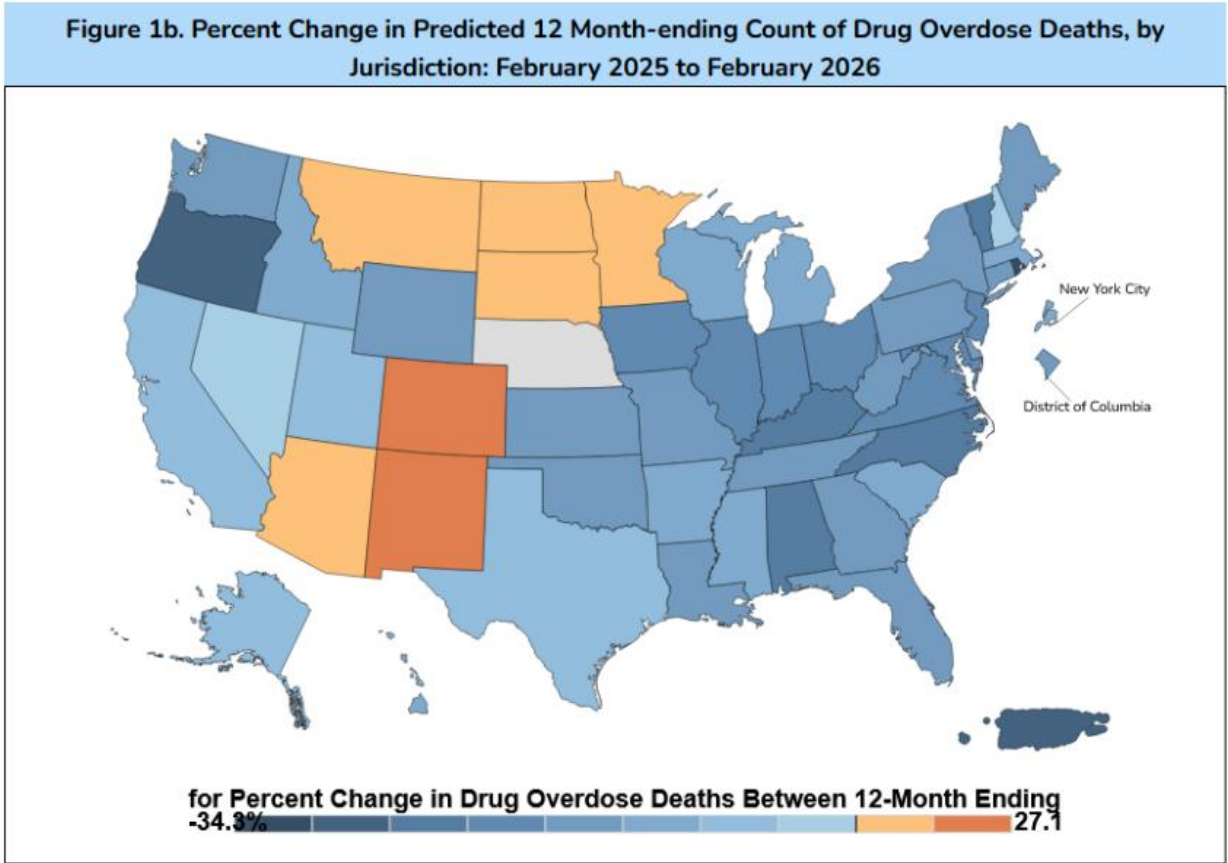
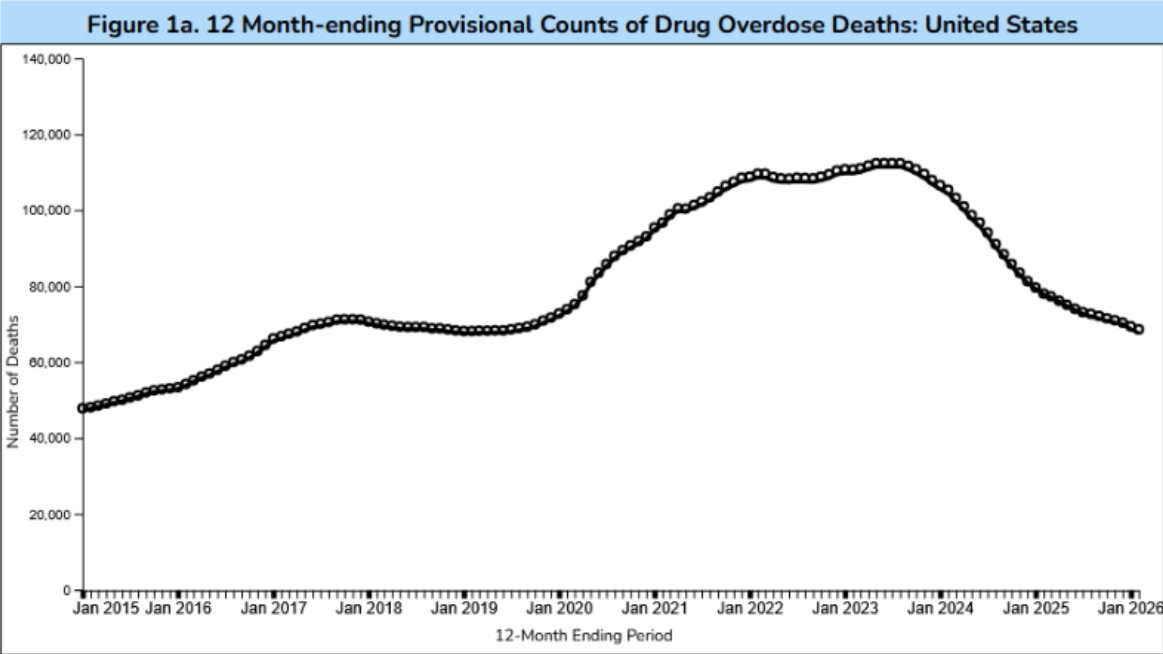
At the conclusion of this, attendees should be able to:

- 1) Explain the history and pharmacology of GLP-1 receptor agonists
- 2) Describe the emerging clinical evidence base supporting the use of GLP-1 receptor agonists for treating SUD in humans
- 3) Evaluate the range of emerging concerns related to the use of GLP-1 receptor agonists for treating SUD



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

Based on data available for analysis on: July 5, 2026



Buprenorphine with robust evidence-base for efficacy, but longer-term outcomes remain sub-optimal

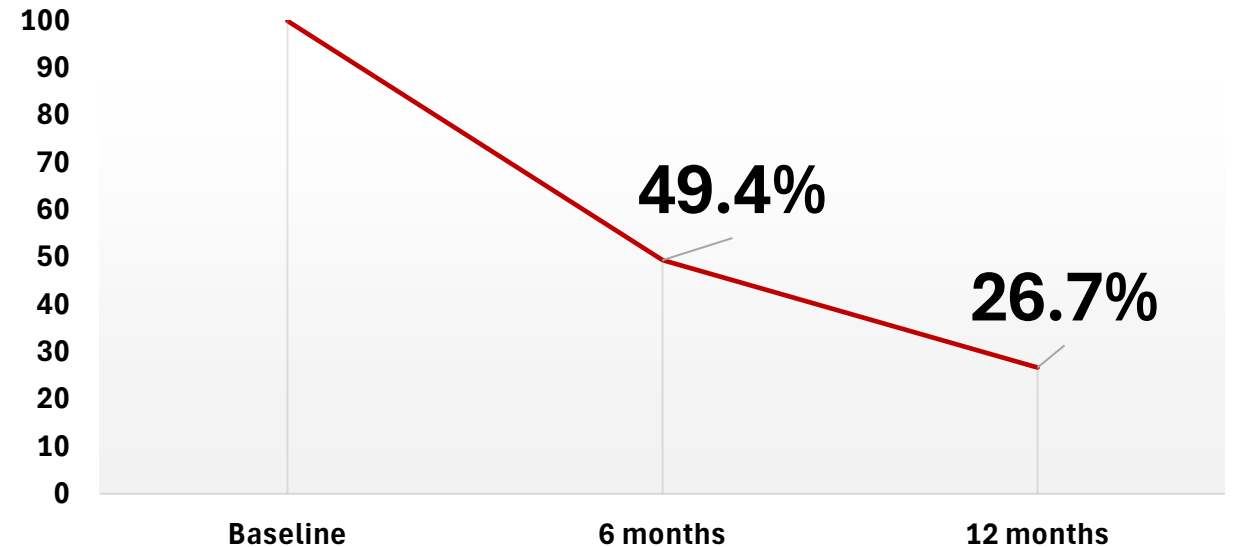


70%

reduction in mortality and overdoses



Buprenorphine treatment retention
(n=58,200)



Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs

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



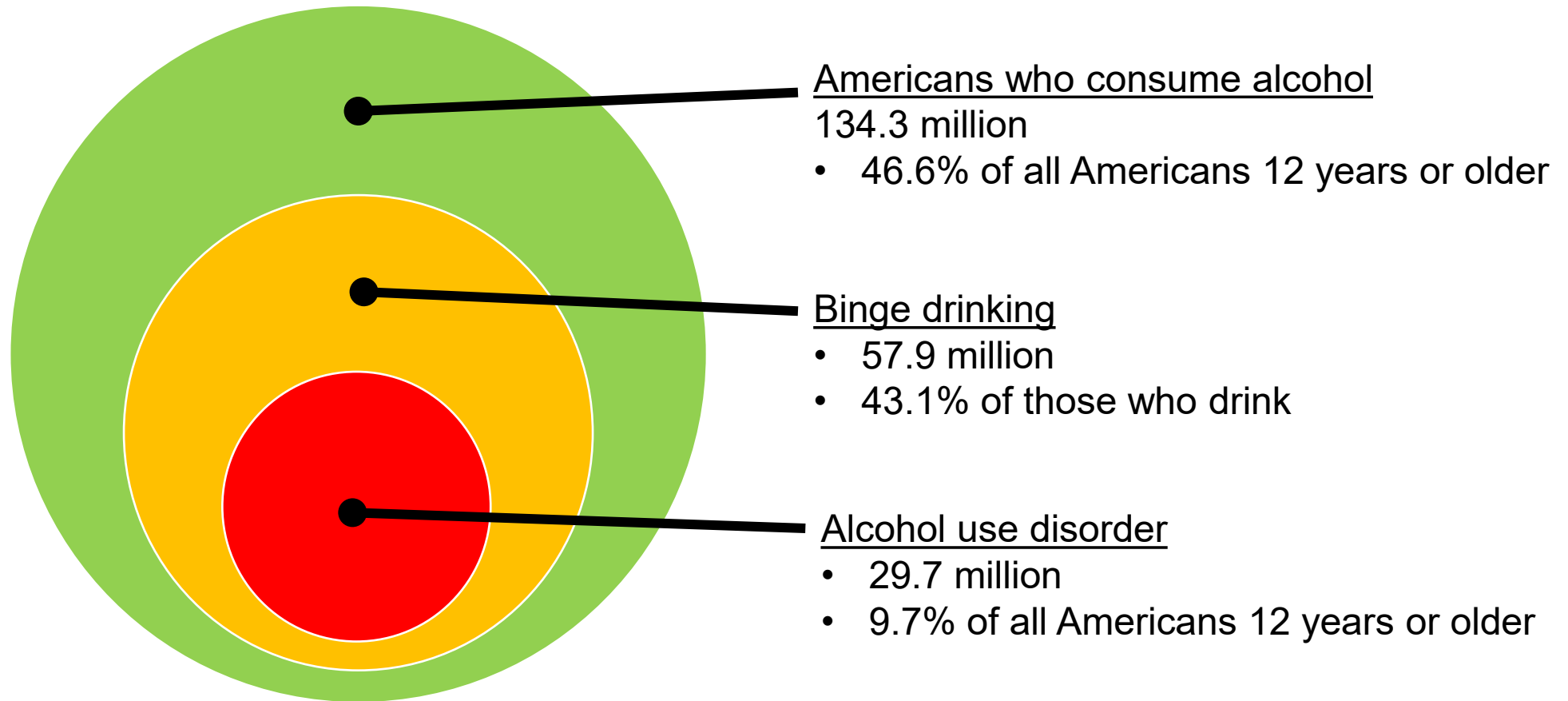
Research Gap

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

Goal

Accelerate availability of
expanded treatment options

Unhealthy alcohol use remains common in the US



MAUDs are good options, but in 2019 only 2.7% of patients with AUD receive any of these

Naltrexone PO

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

AE: dizziness,
somnolence, GI distress,
fatigue

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

Naltrexone IM

Ideally prior PO trial, but
not absolute

AE: Liver toxicity even
less likely; injection site
reaction

Hospital initiation may
be covered by
manufacturer

Acamprosate

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

AE: GI distress

Contraindicated in renal
impairment (CrCl<30)

Disulfiram

Limited to those with
higher motivation for
abstinence

Particularly effective if
incorporate significant
other

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



National Institute on Alcohol Abuse and Alcoholism Strategic Plan:

Fiscal Years 2024–2028

Advancing Alcohol Research to Promote Health and Well-Being



Goal 1: Elucidate the biological mechanisms and consequences of alcohol misuse



Goal 2: Identify patterns, trends, and public health impact of alcohol misuse



Goal 3: Prevent and reduce alcohol misuse, alcohol use disorder, and associated consequences



Goal 4: Improve diagnosis and **expand treatment of alcohol use disorder** and alcohol-related conditions



**The
Economist**

The everything drugs

**It's not just obesity. Drugs like
Ozempic will change the world**

As they become cheaper, they promise to improve
billions of lives

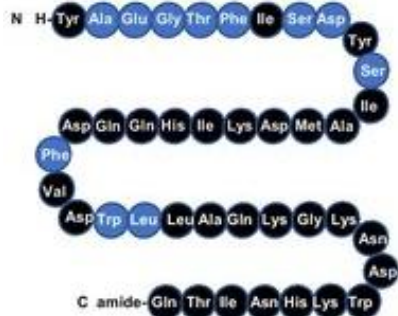
Oct 24, 2024



GLP-1 was one of the first incretins to be discovered

Incretins are group of hormones that are secreted by the small intestines after oral food intake.

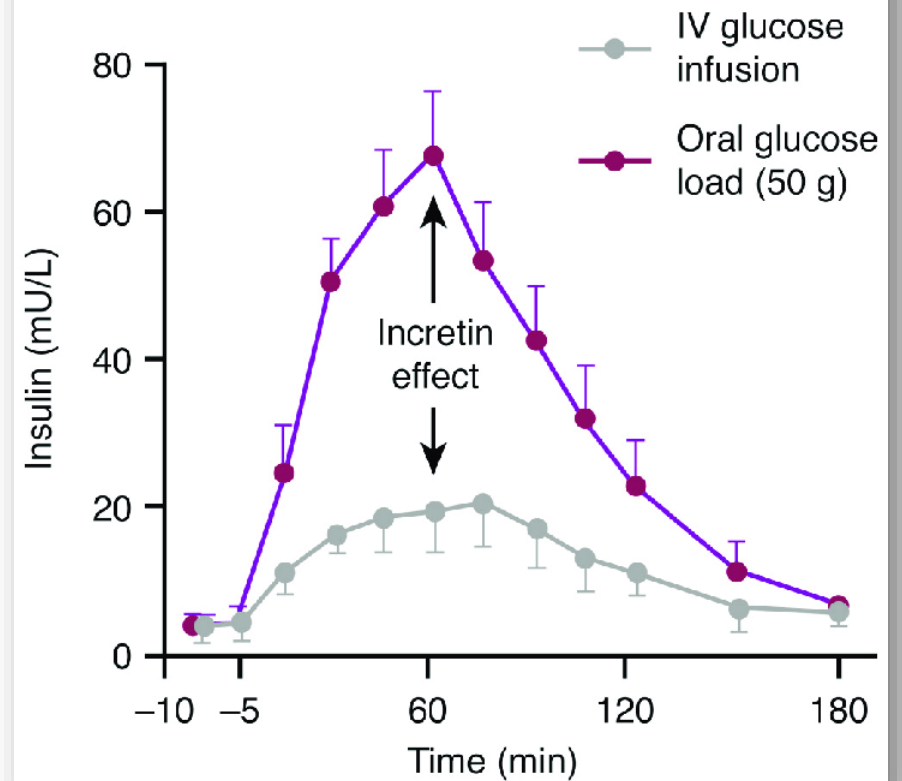
Glucose-dependent
insulinotropic
polypeptide
(GIP)



Glucagon-Like
Peptide-1
(GLP-1)

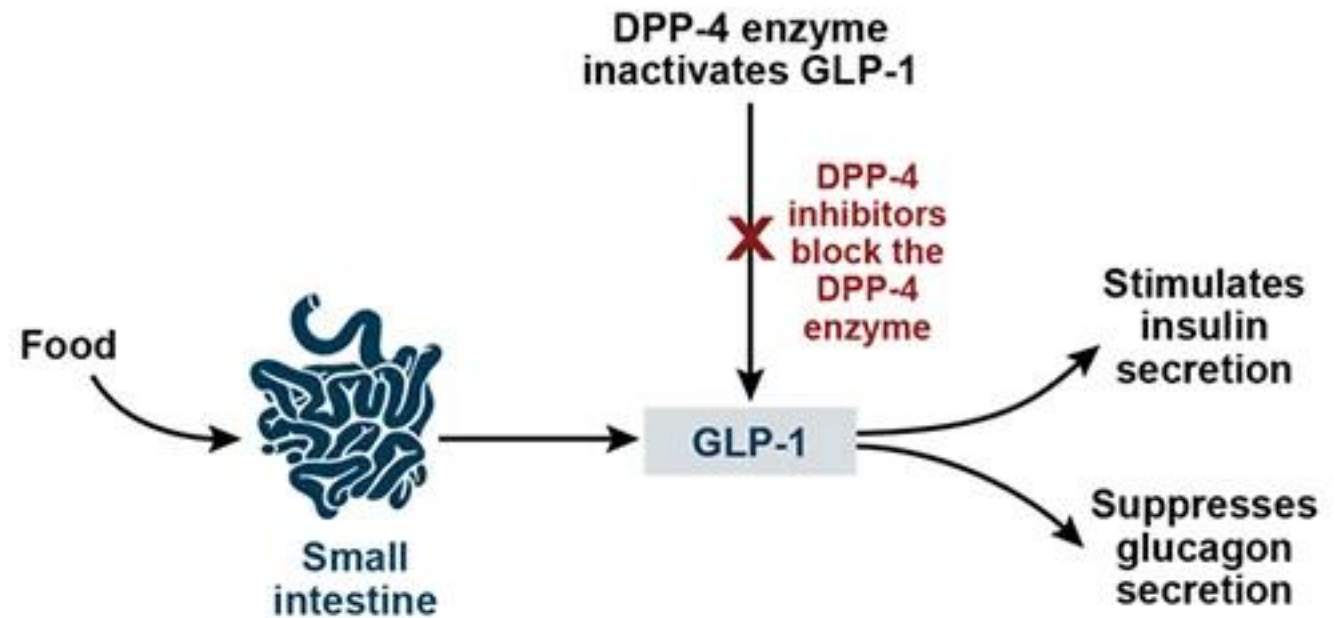


Insulin response



- GLP-1 not thought to be a good target for drug development due to extremely short half life (1-2 minutes).
- Enzyme dipeptidyl peptidase-4 (DPP-4) responsible for deactivating GLP-1
- Inhibiting DPP-4 was therefore the initial strategy, but this never worked well for diabetes treatment.

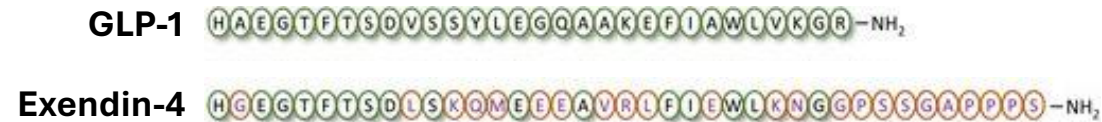
DPP-4 Inhibitors *Mechanism of Action*



Drucker DJ. *Diabetes Care*. 2007;30:1335-1343.

Discovery of exendin paved the way for the modern GLP-1 medications

Discovery in 1991 of **exendin-4**—a 39-amino acid peptide found in the venom of the Gila Monster—spurred the eventual development of GLP-1 receptor agonists.



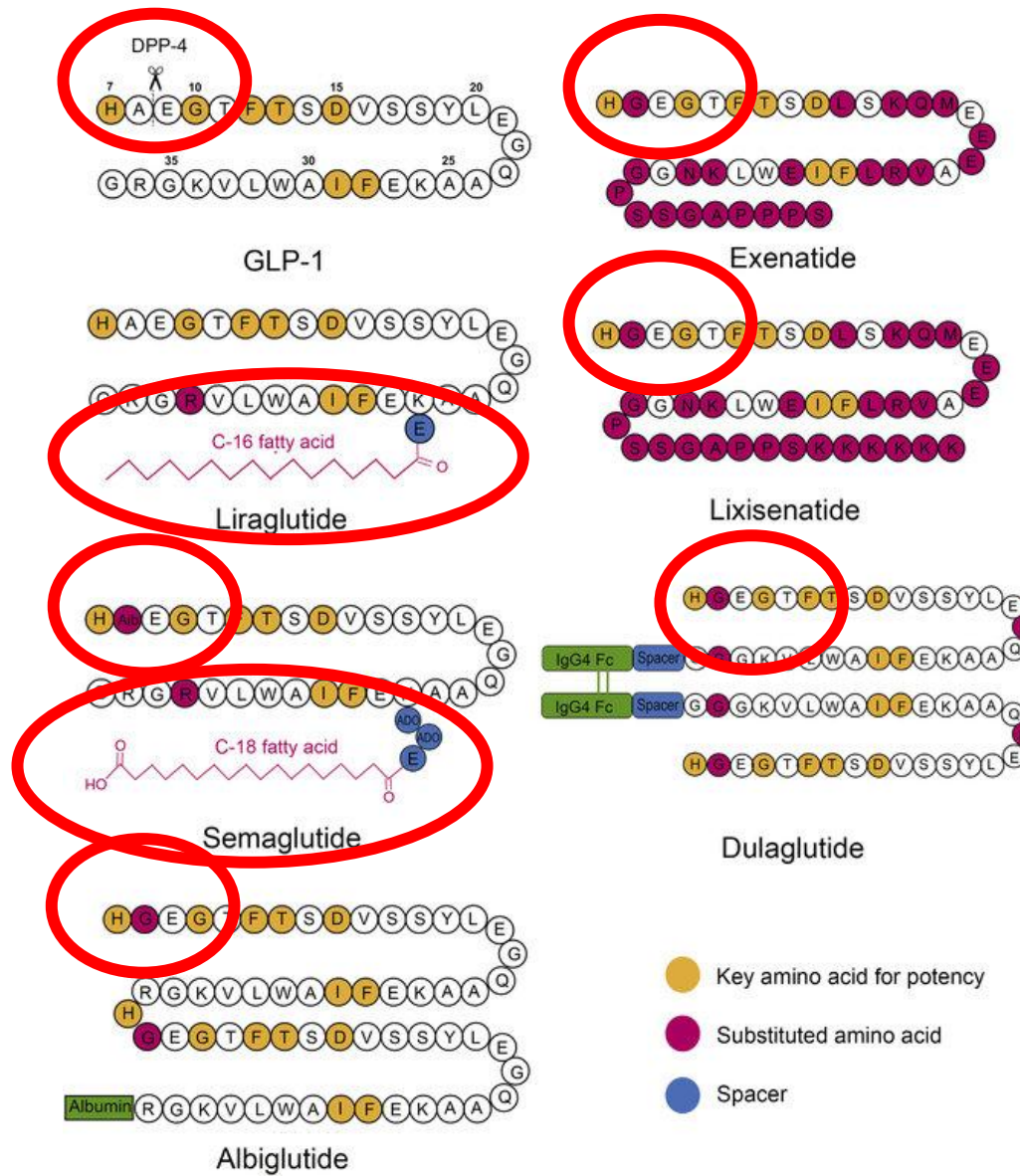
Exendin-4 was structurally similar to human GLP-1, and appeared to resist degradation by the DPP-4 enzyme, leading a much longer half-life.

In humans, exendin-4 had a half-life about 2.4 hours, almost 100 times longer than the native GLP-1!

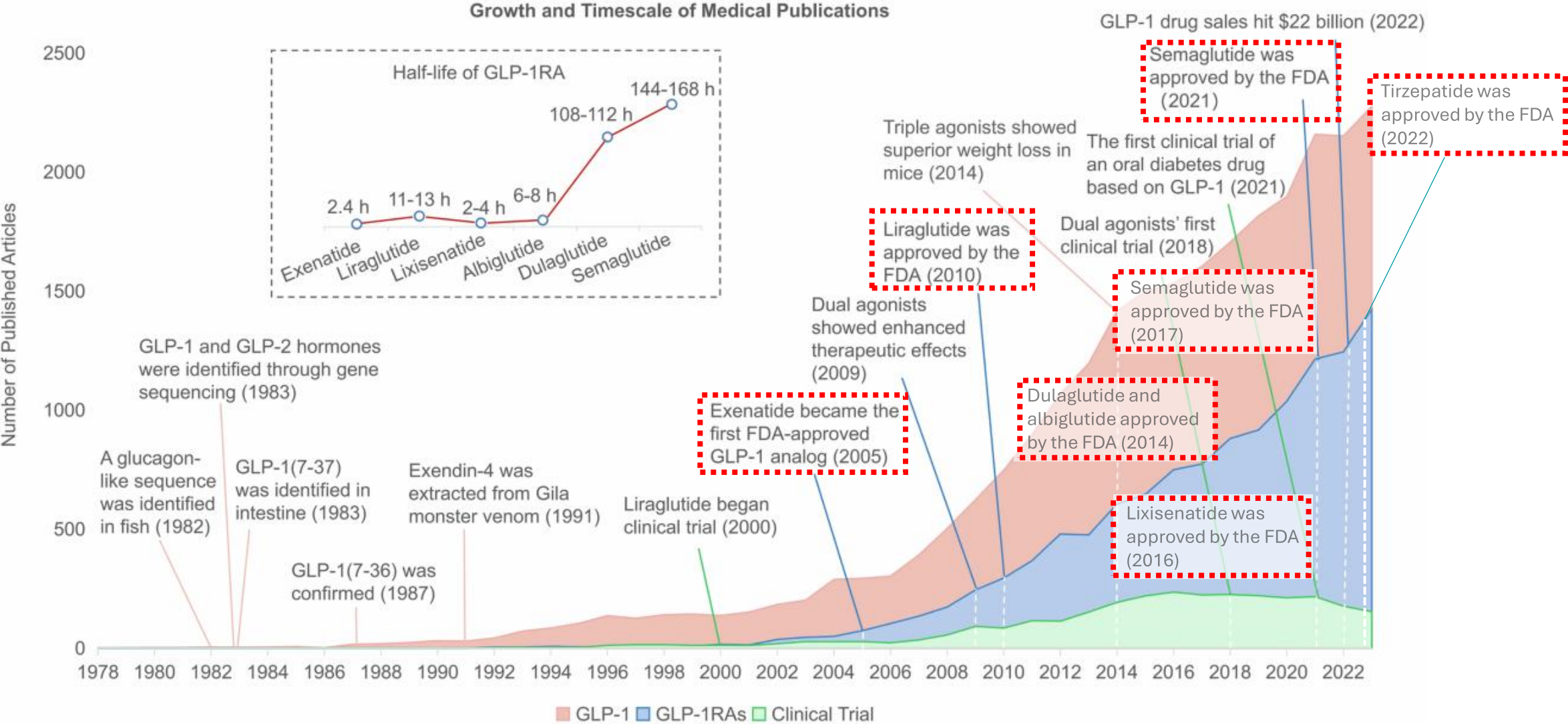
Gila Monster



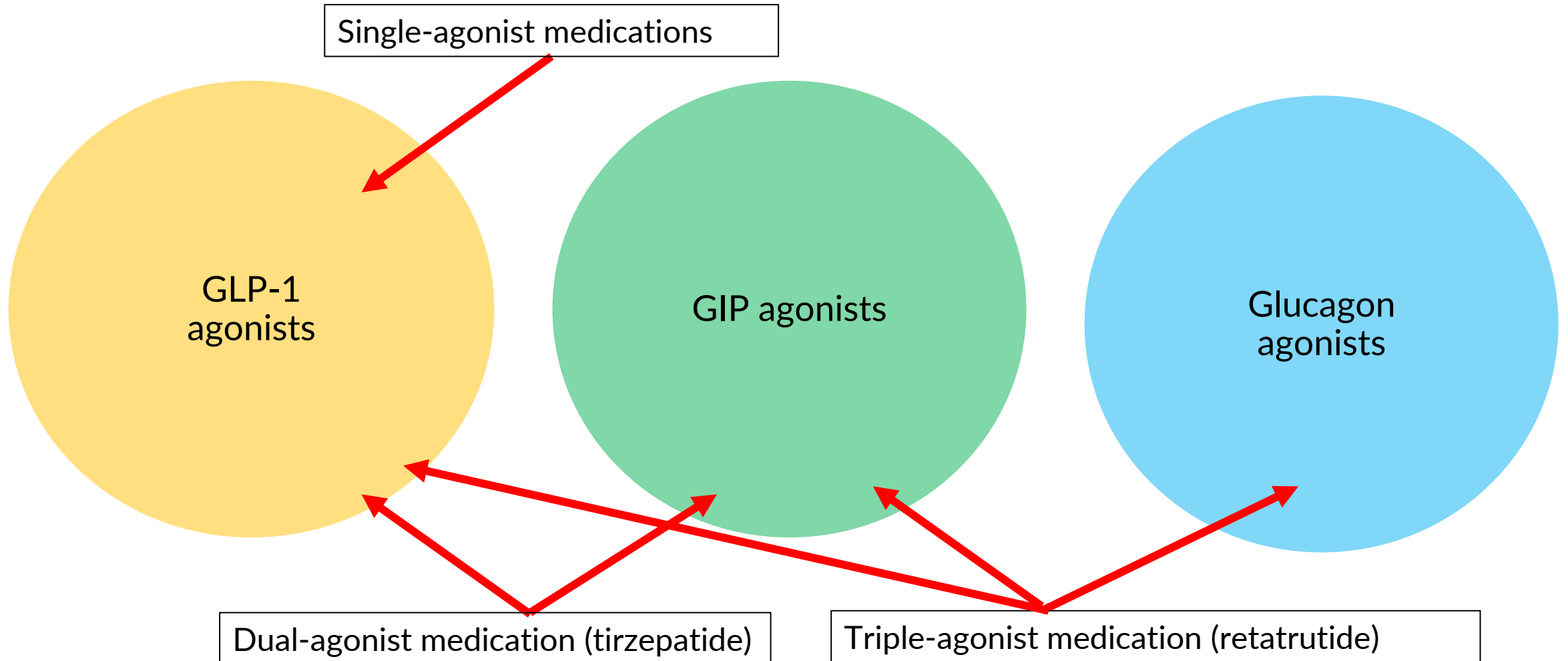
Subsequent research focused on increasing half-life by resisting degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), and enhancing binding to the GLP-1 receptor.



Growth and Timescale of Publications on GLP-1RAs



Most GLP-1RAs have been “single” agonist, but newer ones target multiple receptors, and not always as agonists



↓ Appetite
↑ Neuroprotection?
↑ Satiety

↓ Appetite
↓ Nausea
↑ Neuroprotection?

↓ Hepatic steatosis
↓ Inflammation
↑ Lipid oxidation

↑ Renoprotection
↓ Blood pressure

↓ Gut motility
↓ Gut dysbiosis
↓ Inflammation

↑ Lipid storage
↓ Inflammation

□ GLP-1

□ GIP

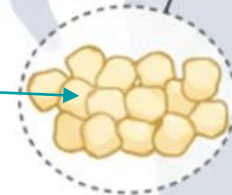
↑ Cardioprotection
↑ Cardiac function
↑ Heart rate

↓ Gastric emptying

↑ Insulin secretion
↑ B-cell proliferation
↓ Glucagon secretion

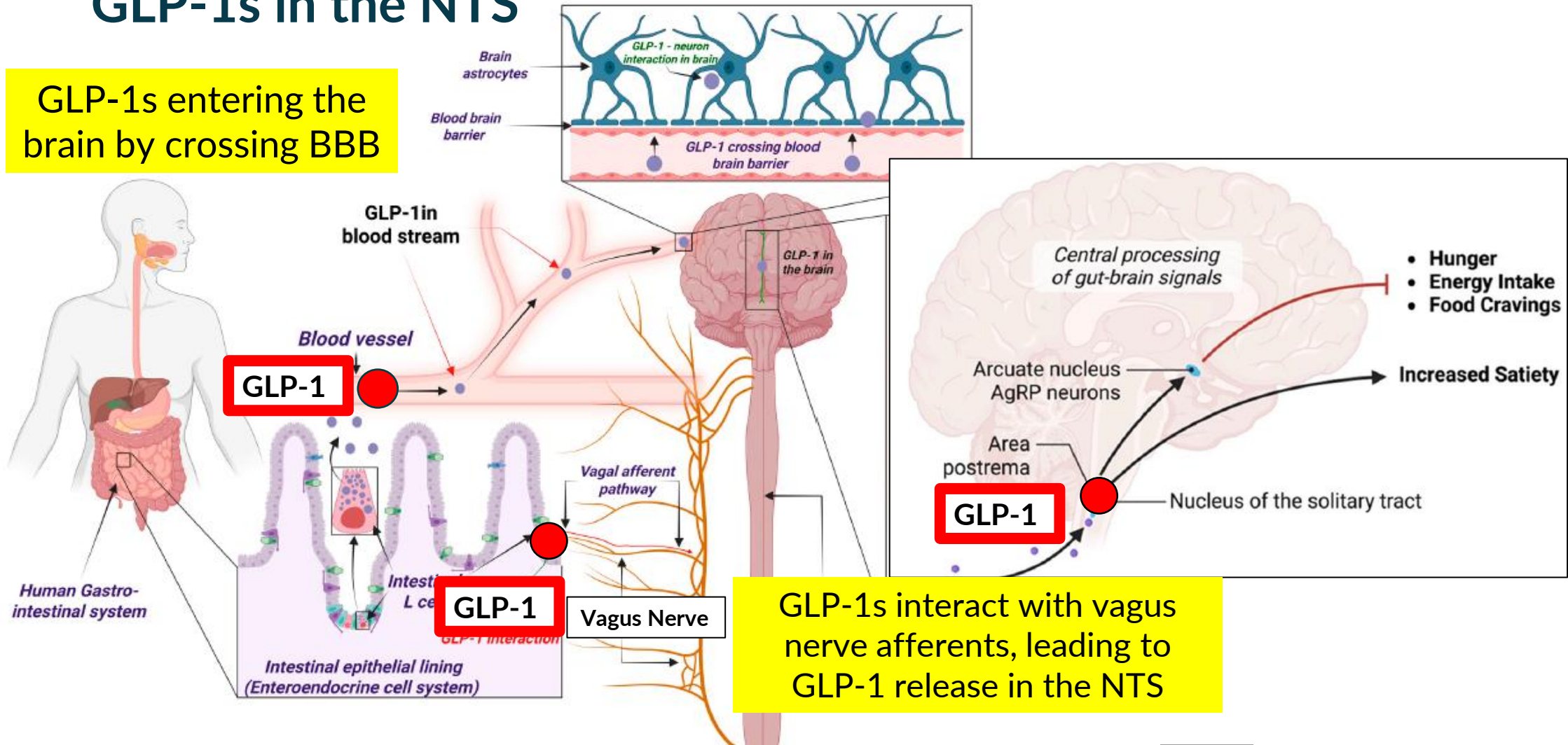
↑ Insulin secretion
↑ B-cell proliferation
↑ Glucagon secretion

↓ Bone resorption



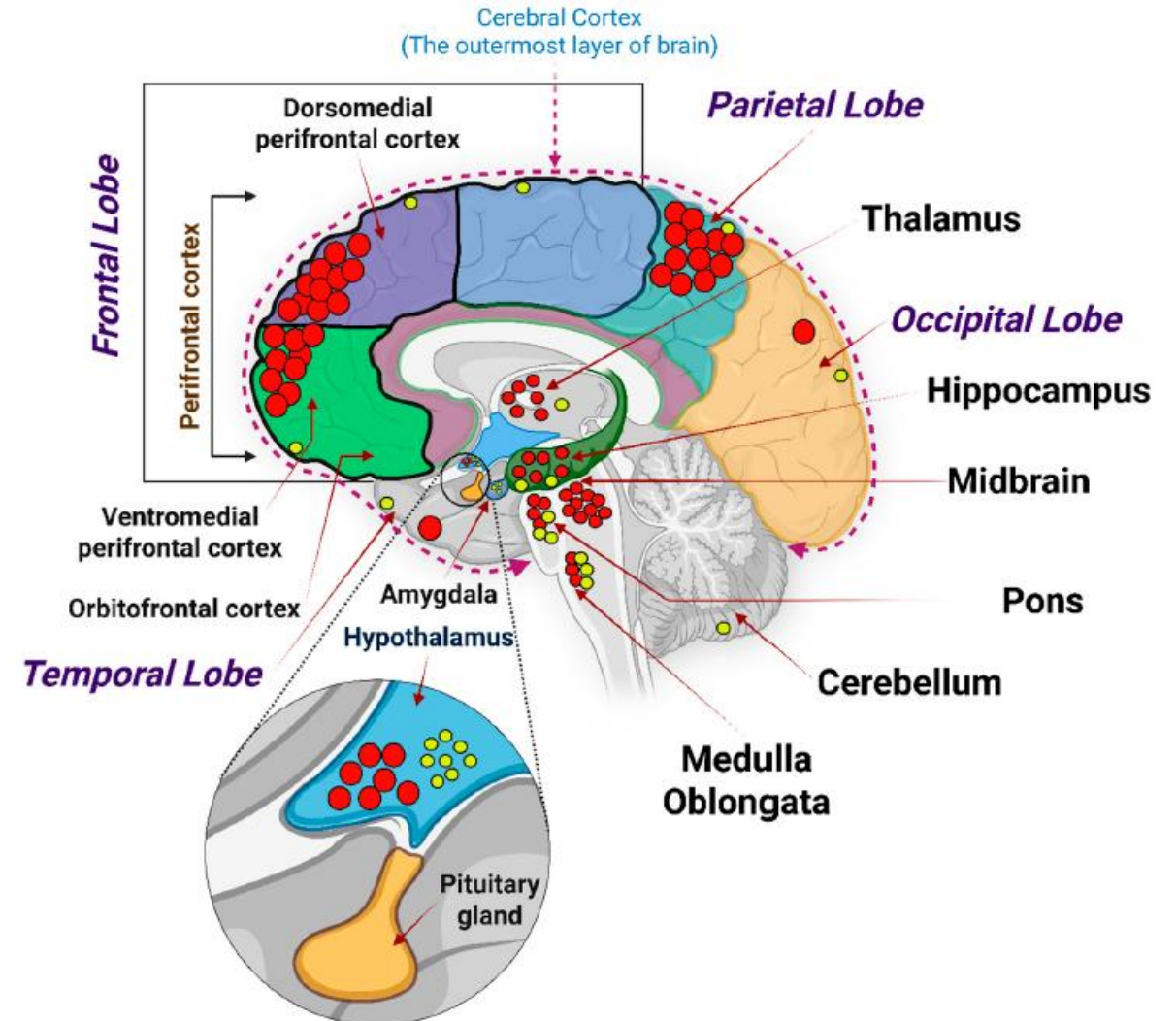
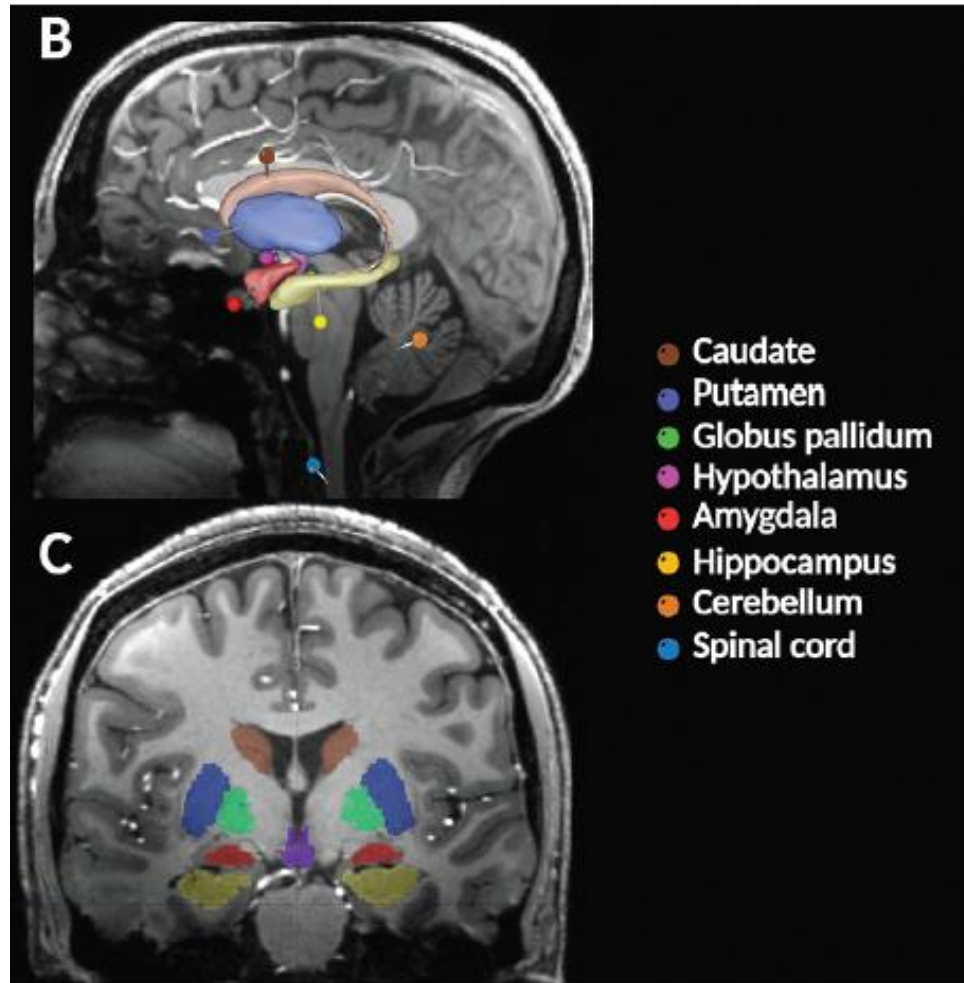
Peripherally Released GLP-1s Access the Brain Directly and Indirectly, but the Brain Produces its Own GLP-1s in the NTS

GLP-1s entering the brain by crossing BBB

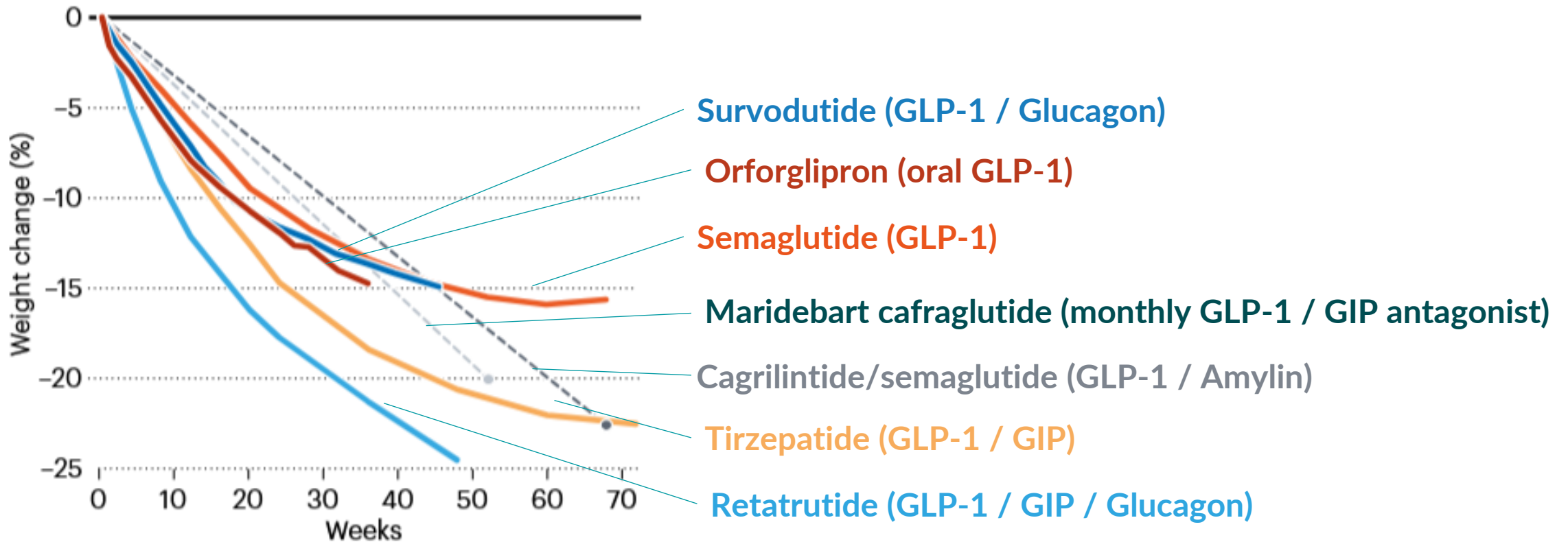


GLP-1s interact with vagus nerve afferents, leading to GLP-1 release in the NTS

GLP-1 receptors are widely found in the brain, particularly in the reward-related regions.



Next-generation obesity drugs are arriving soon



*Data are from company reports of the most recent trials, with no intermediate data available for CagriSema (cagrilintide and semaglutide) or MariTide (maridebart cafraglutide). Data are not placebo-adjusted.



Neurobiological model of substance use disorders



Disrupted self-processing

- Maladaptive self-referential thoughts
- Default mode network

Self-referential
rumination



Operant Conditioning

- "Liking"
- Reward network

Binge/
intoxication



Opponent-process

- Reward vs anti-reward
- Stress

Withdrawal/
Negative affect



Incentive sensitization

- "Craving" and "Wanting"
- Salience network

Pre-occupation/
Anticipation



Impaired regulation

- Poor inhibitory control
- Executive network

Loss of control

Cravings and stress/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

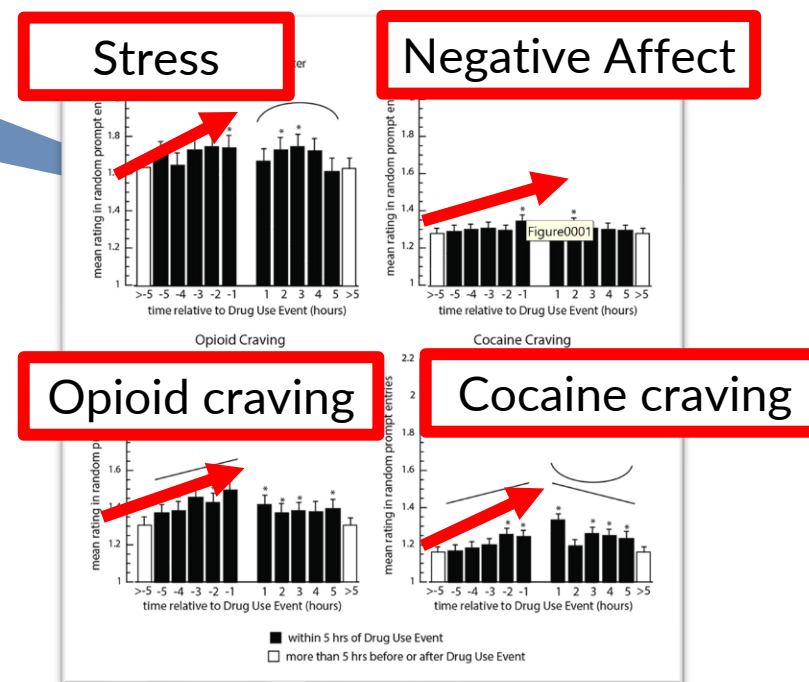
Setting: Outpatient treatment center in Baltimore

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

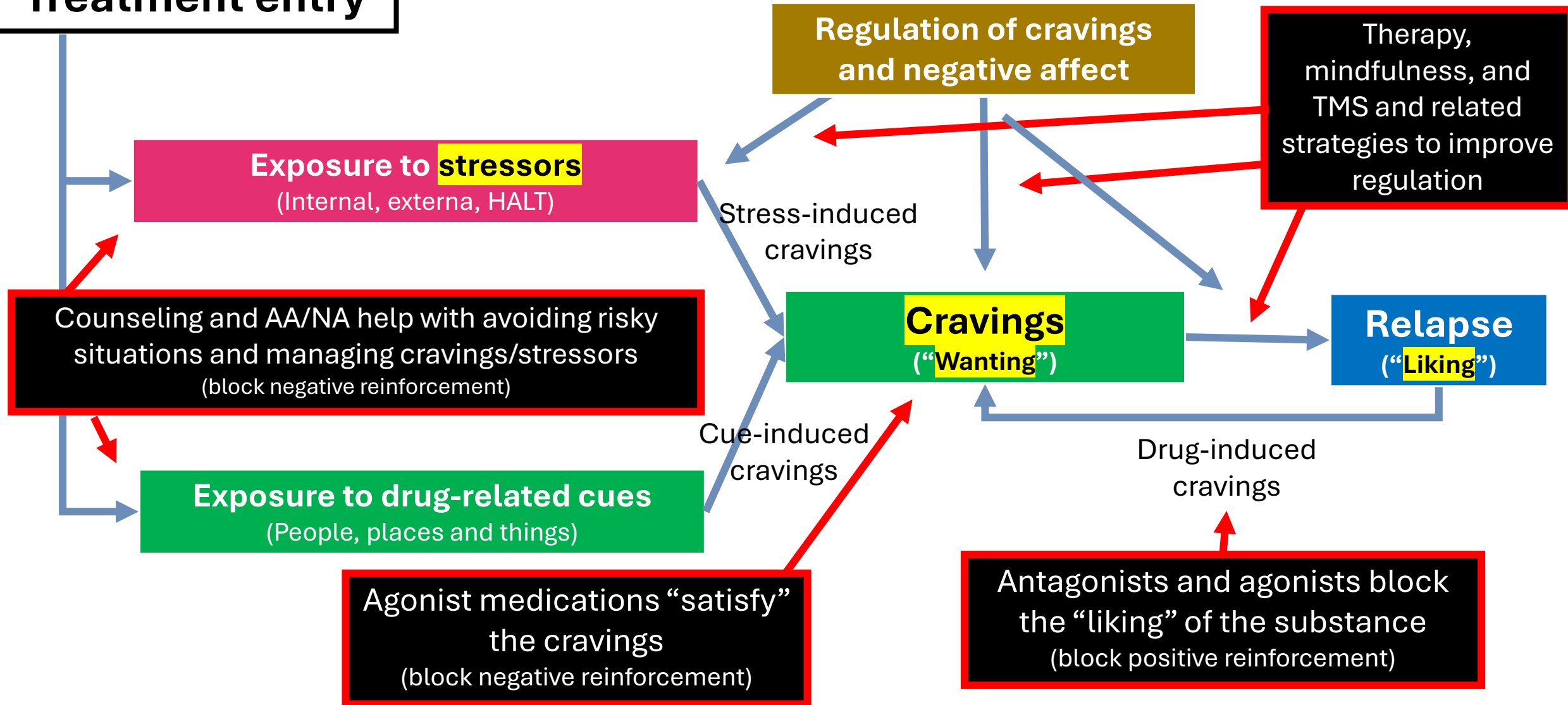
Results: Stress, cravings, and negative mood were higher prior to use events



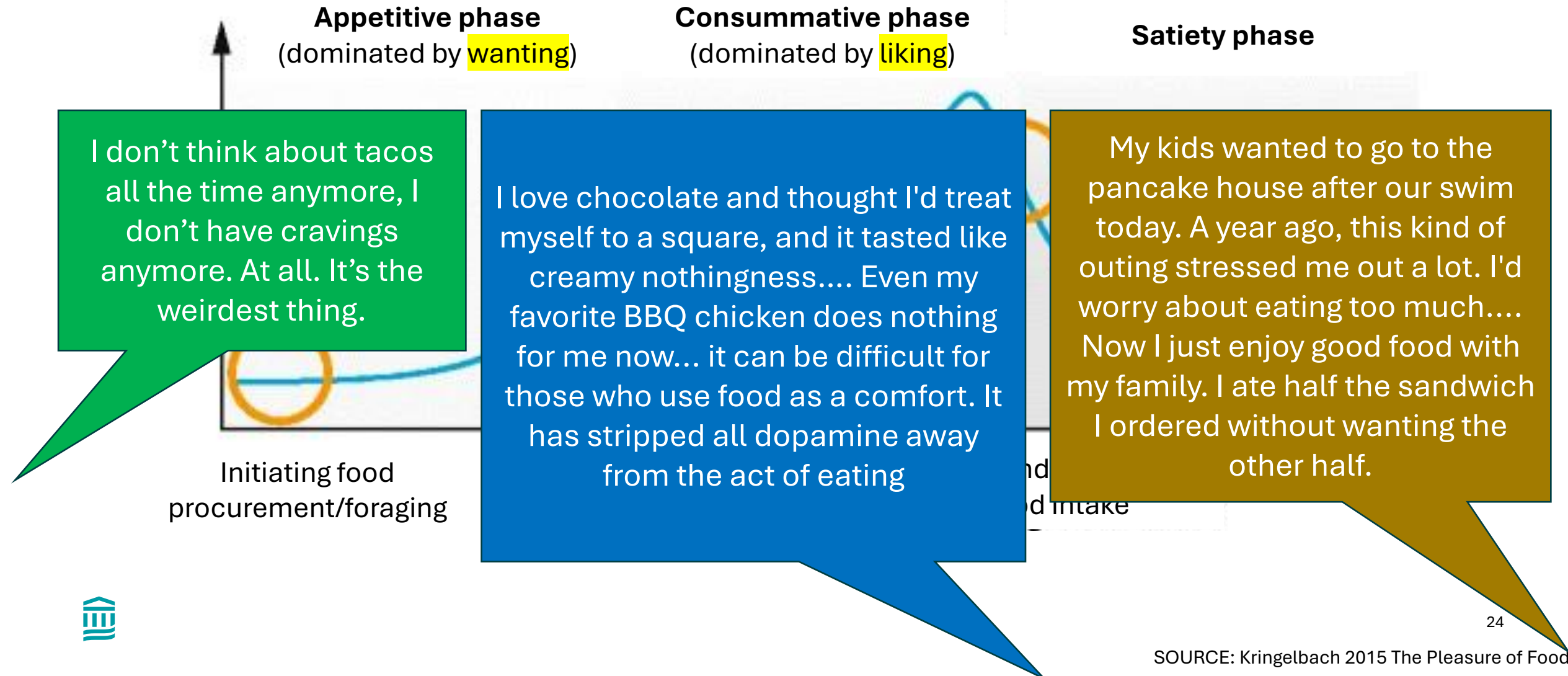
Conclusion: Stress, cravings, and negative mood are increasing prior to use events



Treatment entry



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 2.5mg qwk; all received varenicline and counseling	No difference in smoking

Conclusions:

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



More promising results from RCT of semaglutide for AUD... but trial conducted with non-treatment seekers

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.
- Dosing: 0.25mg x 4 wks, → 0.5mg x 4 wks, → 1.0mg x 1 wk.

Primary outcomes:

- Alcohol consumption in a laboratory self-administration paradigm (consume alcohol ad lib)

Secondary outcomes:

- Alcohol use (drinking days, heavy drinking days (HDD), etc)
- Alcohol 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.



Positive results for semaglutide for AUD in second RCT

Table. Pretreatment Characteristics by Treatment Group for All Randomized Participants

Characteristic	Mean (SD)		
	Placebo	Semaglutide	Total
Randomized, No.	24	24	48
Sex, No.(%)			
Female	17 (71)	17 (71)	34 (71)
Male	7 (29)	7 (29)	14 (29)
Age, y	39.0 (10.9)	40.6 (10.5)	39.9 (10.6)
Race, No.(%) ^a			
Asian	2 (8)	0	2 (4)
Black/African American	4 (17)	3 (13)	7 (15)
Hawaiian/Pacific Islander	0	0	0
White	18 (75)	21 (88)	39 (81)
Alcohol consumption ^b			
Drinks/calendar day	3.0 (1.7)	2.7 (1.7)	2.9 (1.7)
Drinks/drinking day	4.5 (2.5)	3.8 (1.8)	4.2 (2.2)
Drinking days	19.6 (5.5)	20.8 (6.8)	20.2 (6.1)
Heavy drinking days	9.8 (5.5)	8.4 (7.9)	9.1 (6.8)
Alcohol craving, PACS score	12.2 (6.5)	11.9 (4.7)	12.0 (5.6)
Current smoking, No.(%) ^c	7 (29)	6 (25)	13 (27)
Cigarettes per day	14.0 (13.5)	8.0 (7.7)	11.2 (11.2)

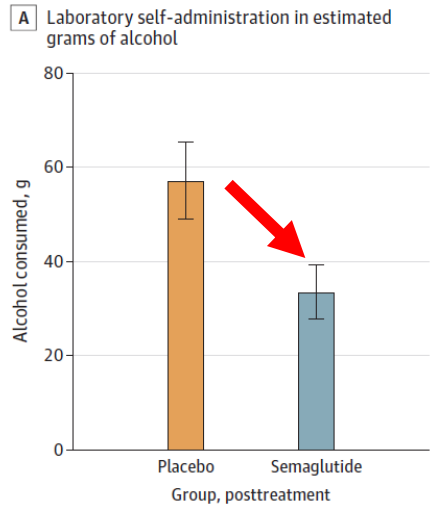


Positive results for semaglutide for AUD in second RCT

Results:

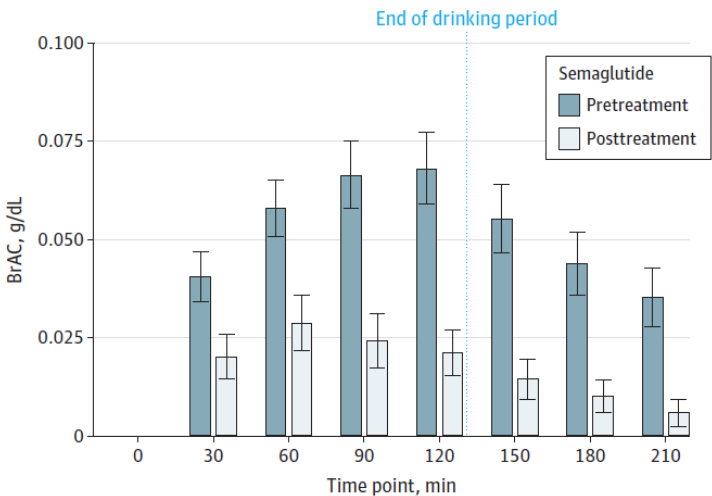
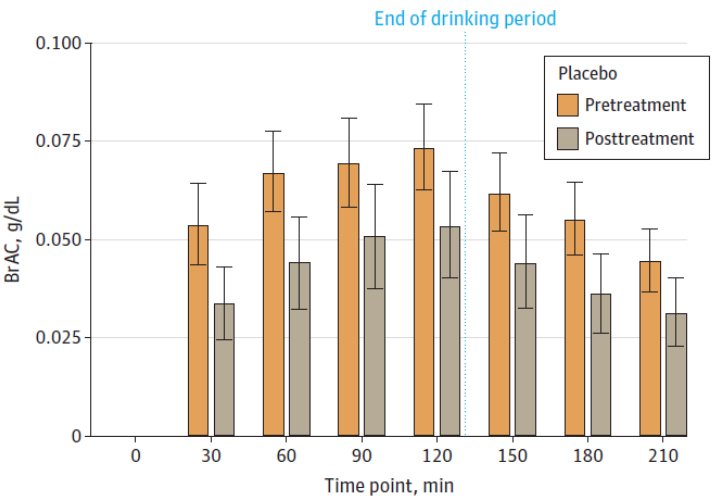
- **Significant reduction** in laboratory self-administration task

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**

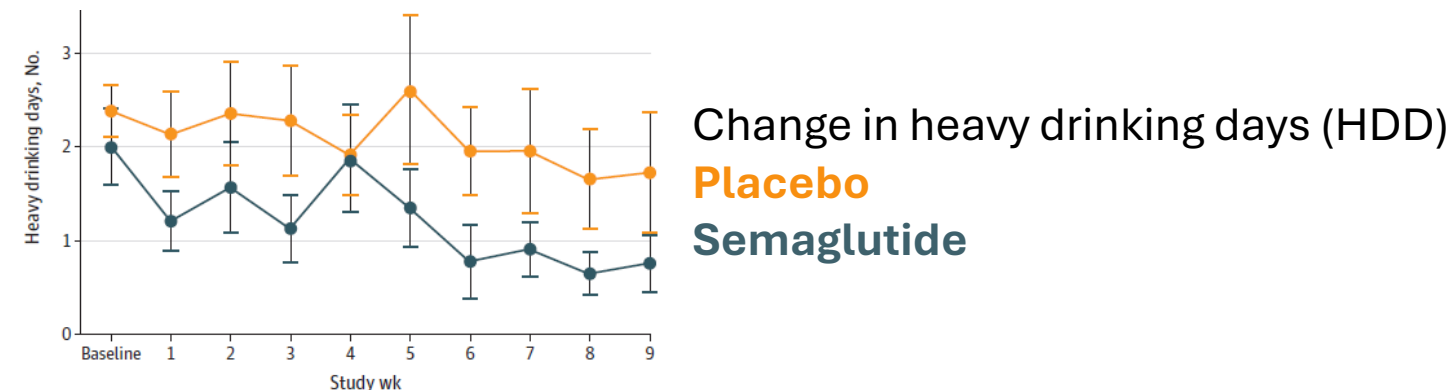
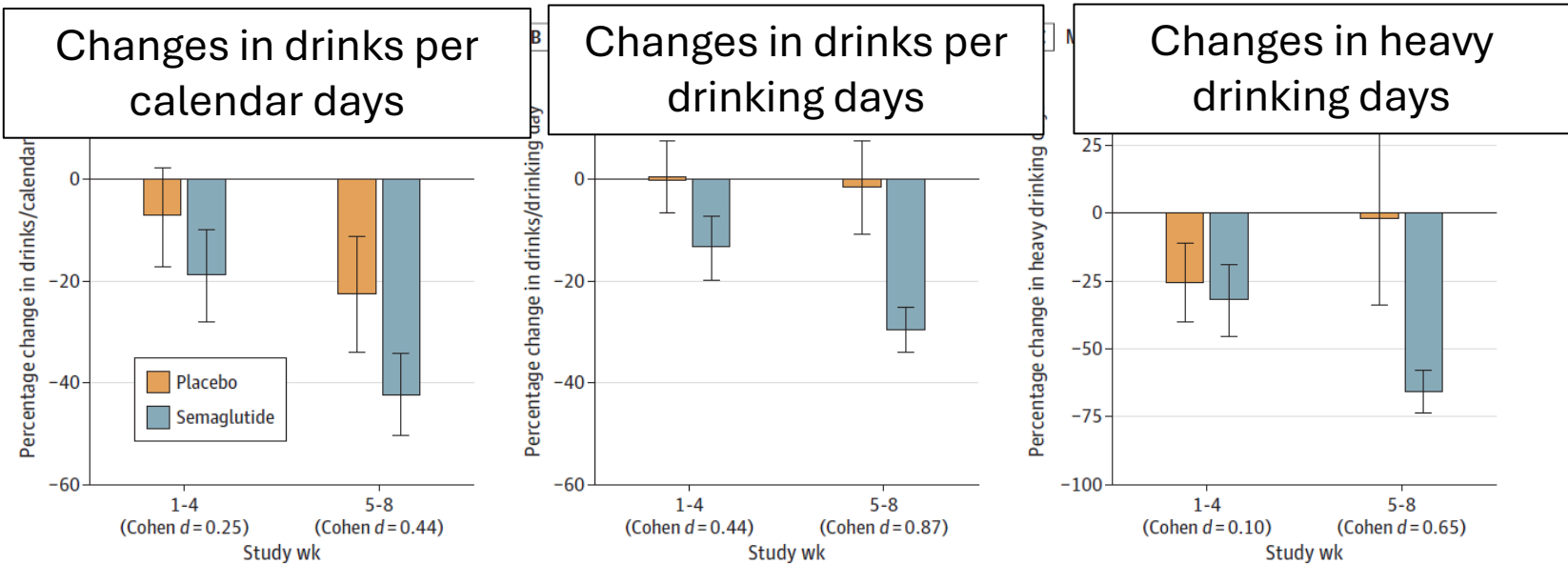


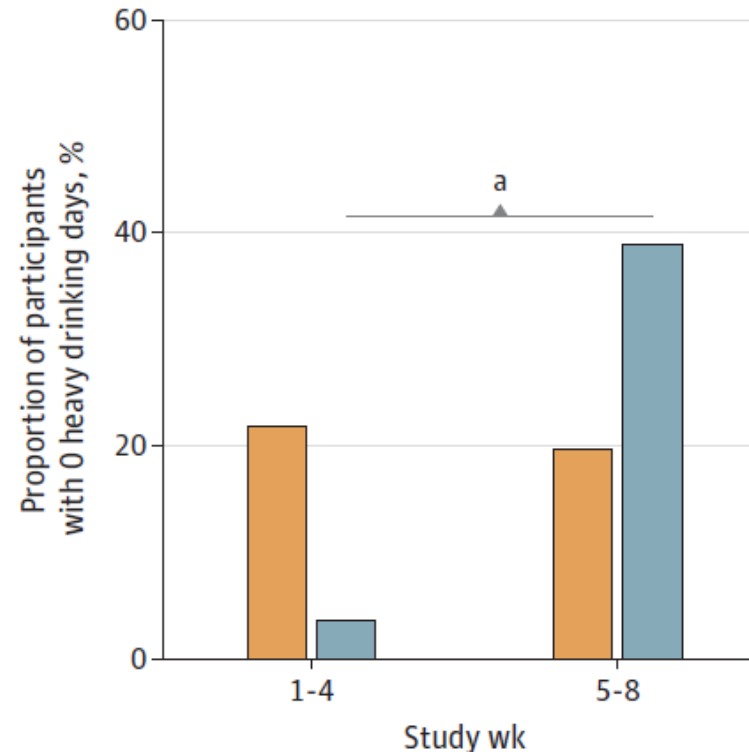
Figure 4. Medication Group Differences in Weekly Drinking and Craving as a Function of Treatment Period



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**



Proportion of participants with ZERO heavy drinking days (HDD)

Placebo

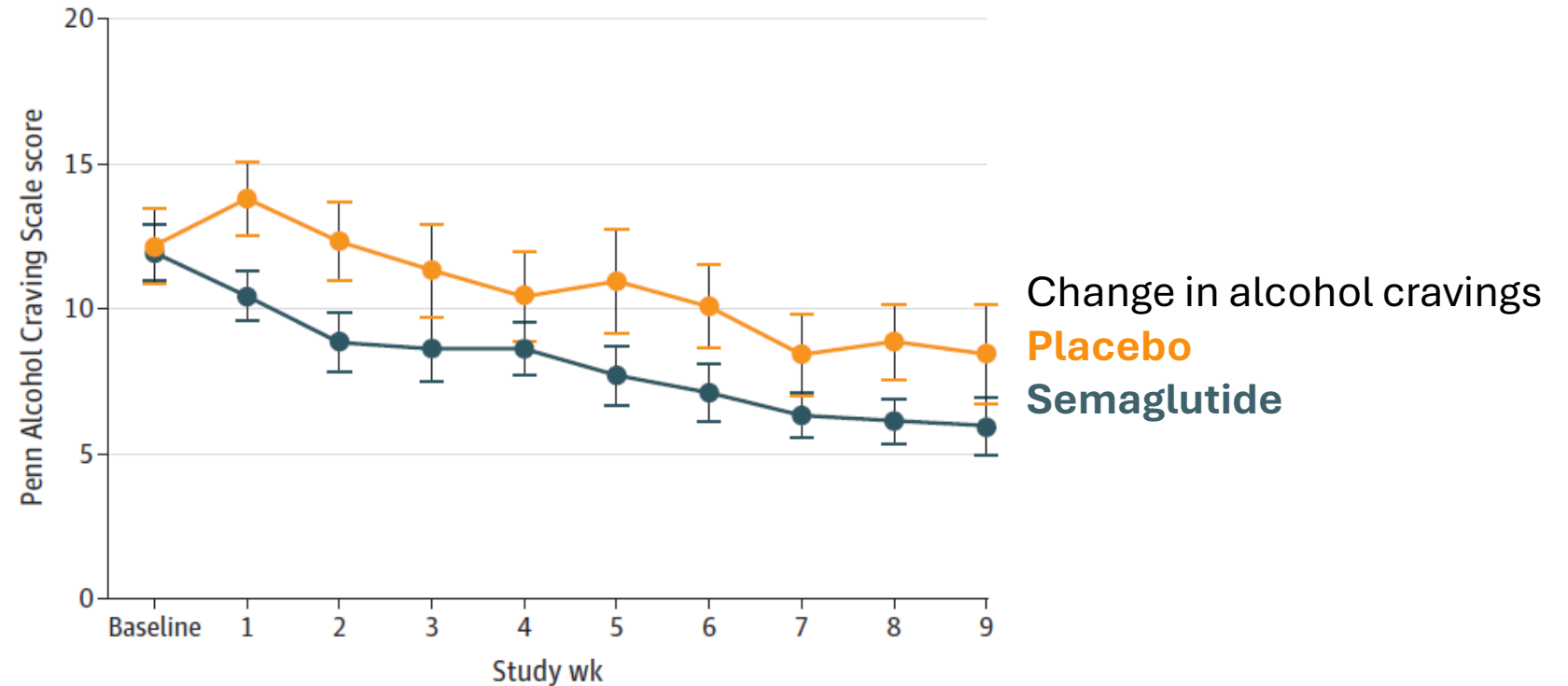
Semaglutide



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 (7.2)	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)

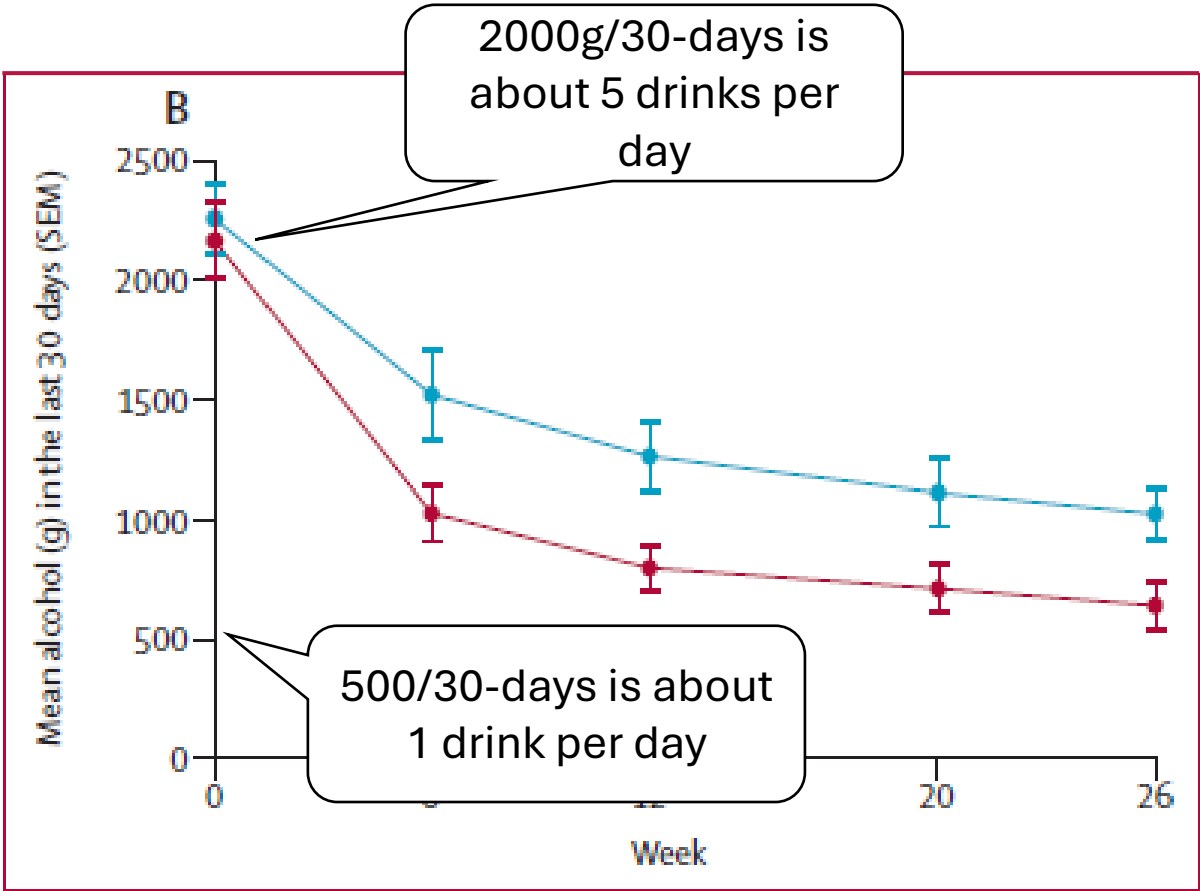
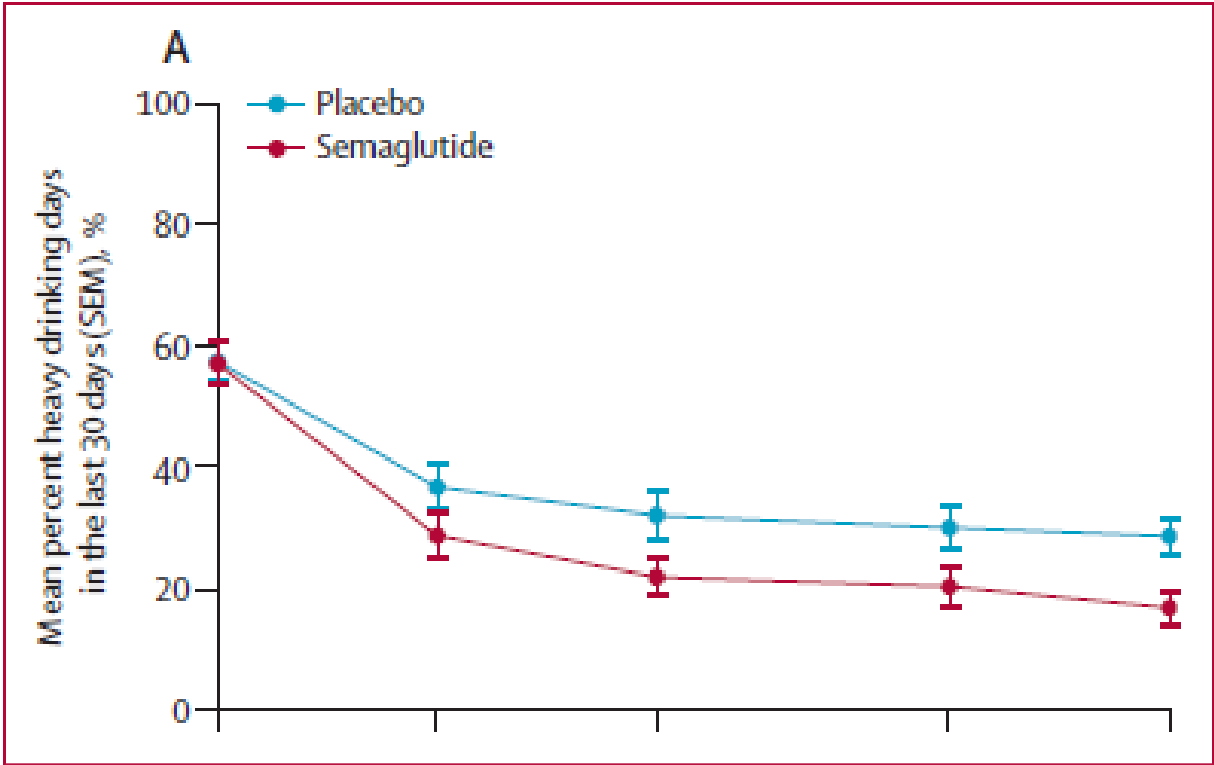


Second RCT of semaglutide for AUD... first to enroll treatment seekers

	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.

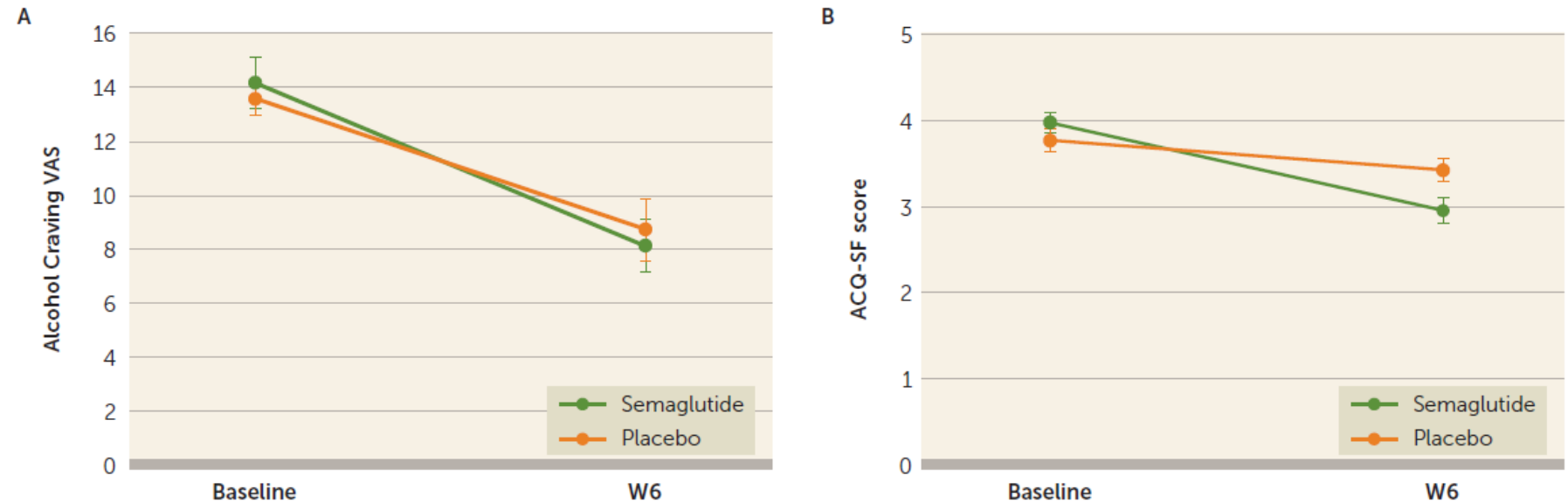


Third RCT of semaglutide for AUD using the oral formulation

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).

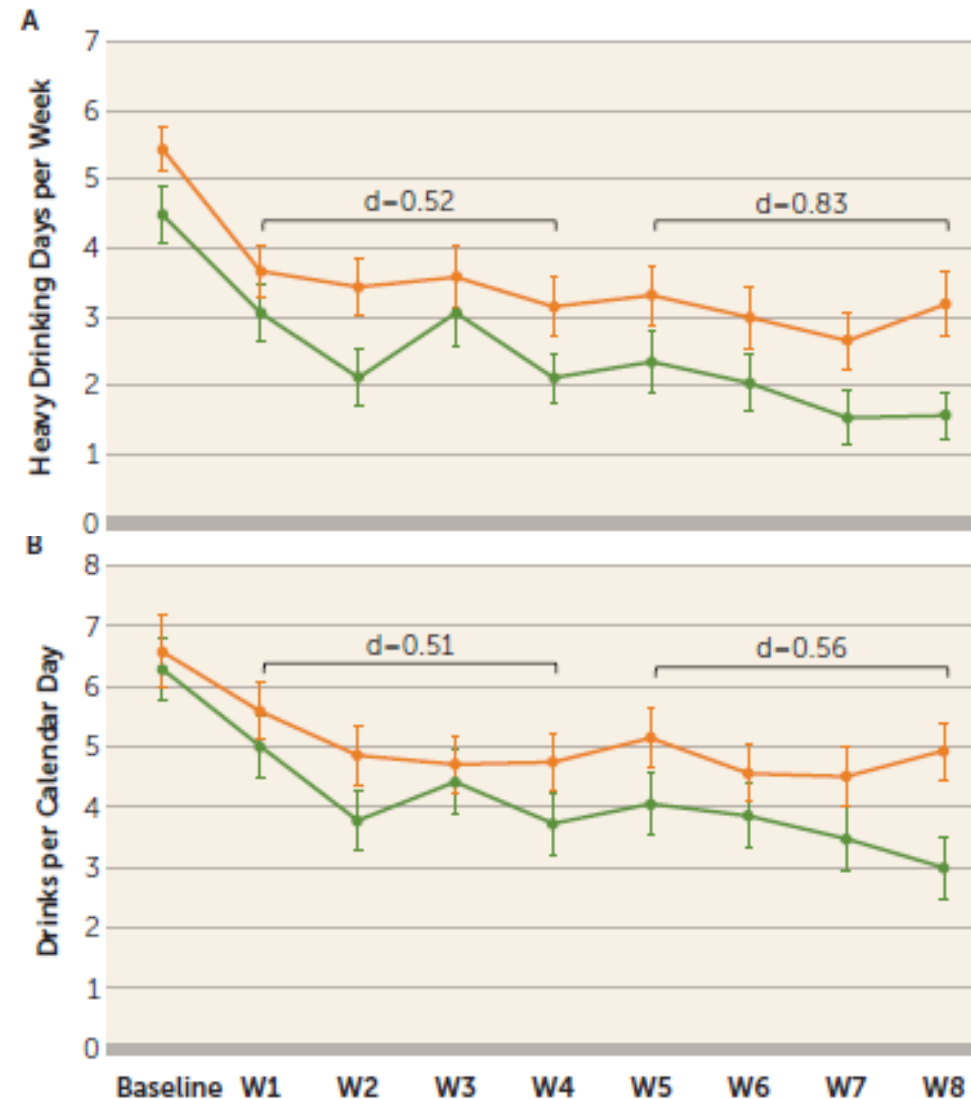
FIGURE 2. Alcohol cue-elicited craving at baseline and week 6 by treatment group^a



Third RCT of semaglutide for AUD using the oral formulation

Results:

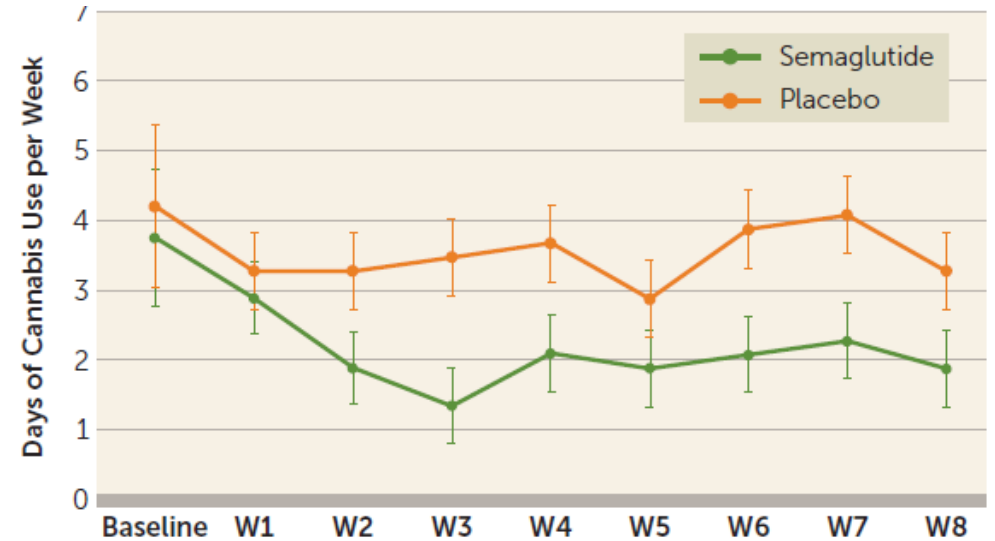
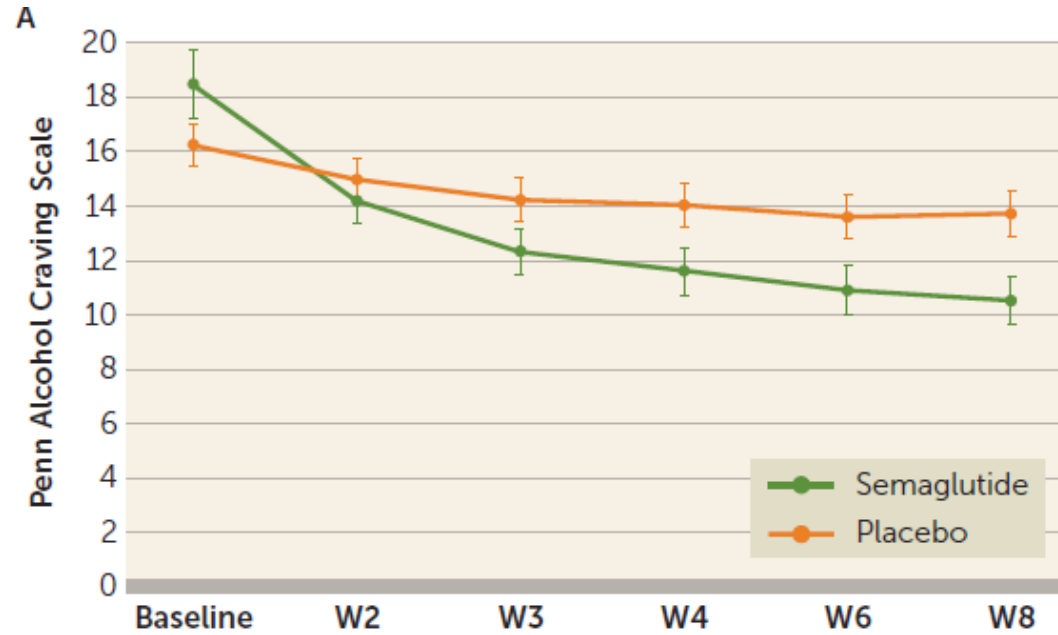
- Overall, **significant reduction in Heavy Drinking days** but not drinking days or drinks per day



Third RCT of semaglutide for AUD using the oral formulation

Results:

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



Schacht et al Am J Psych 2026

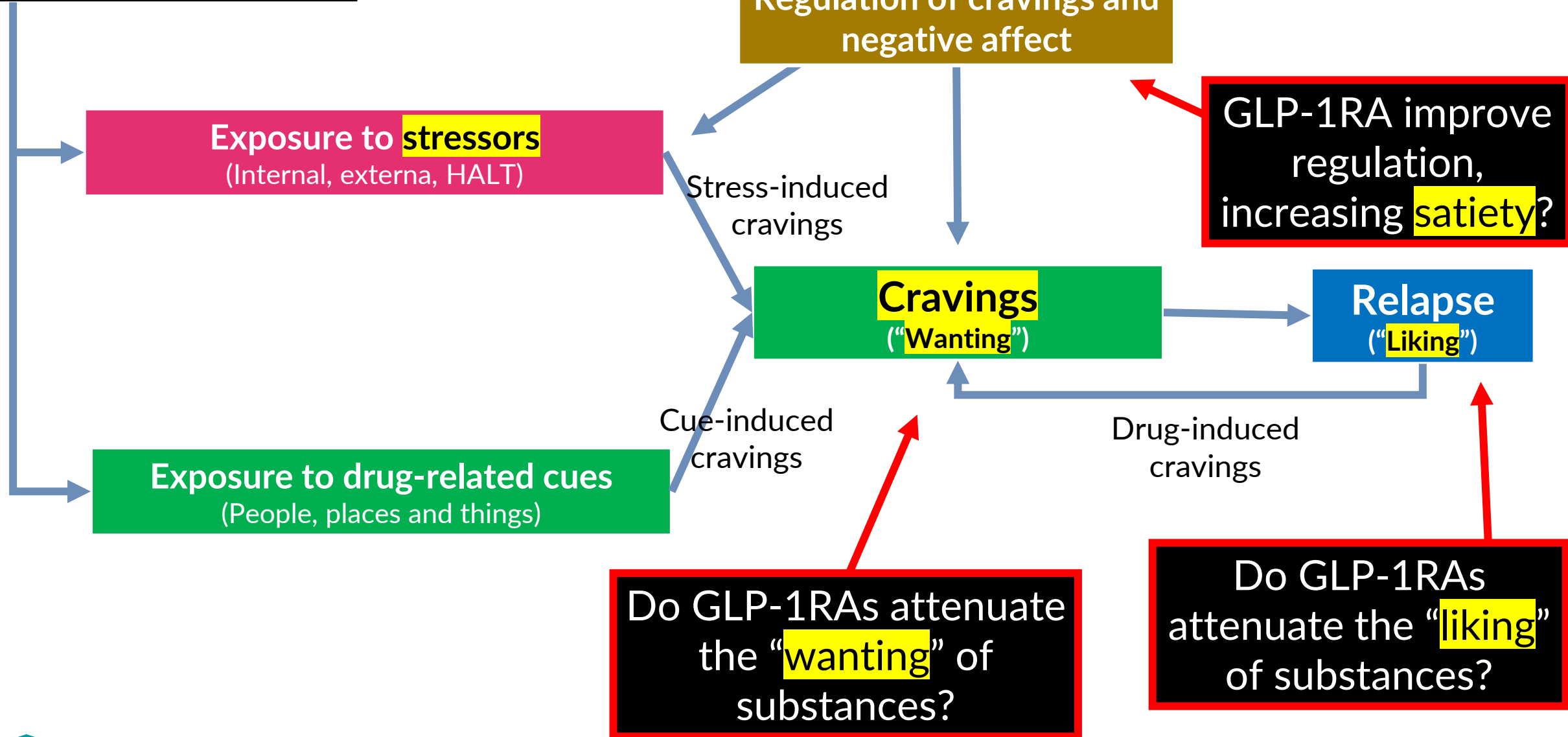


So we have 3 RCTs for semaglutide for AUD, all positive!

- 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 Schact trials enrolled those with obesity/overweight



Treatment entry



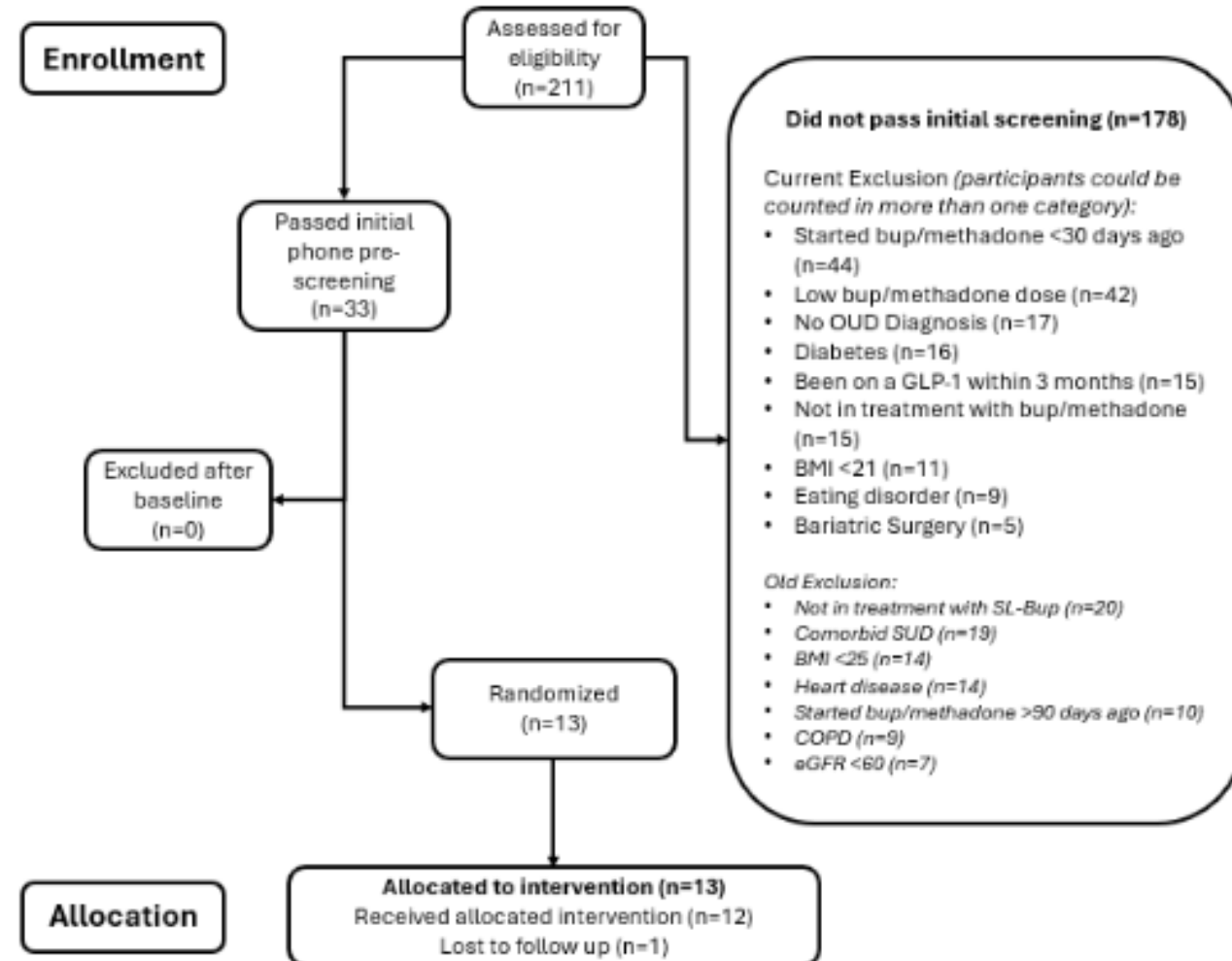
Ongoing clinical trials at BWH

Semaglutide for the treatment of OUD

- NIDA-funded (R21DA060304)
- 12-week, double-blind, placebo-controlled, randomized trial of individuals with OUD to receive either weekly injections of semaglutide or placebo.
- Recruit individuals (n=46) on MOUD either buprenorphine or methadone permitted
- **Aim 1:** Determine the effects of semaglutide on opioid cue-reactivity.
- **Aim 2:** Assess the safety and preliminary efficacy of semaglutide for OUD



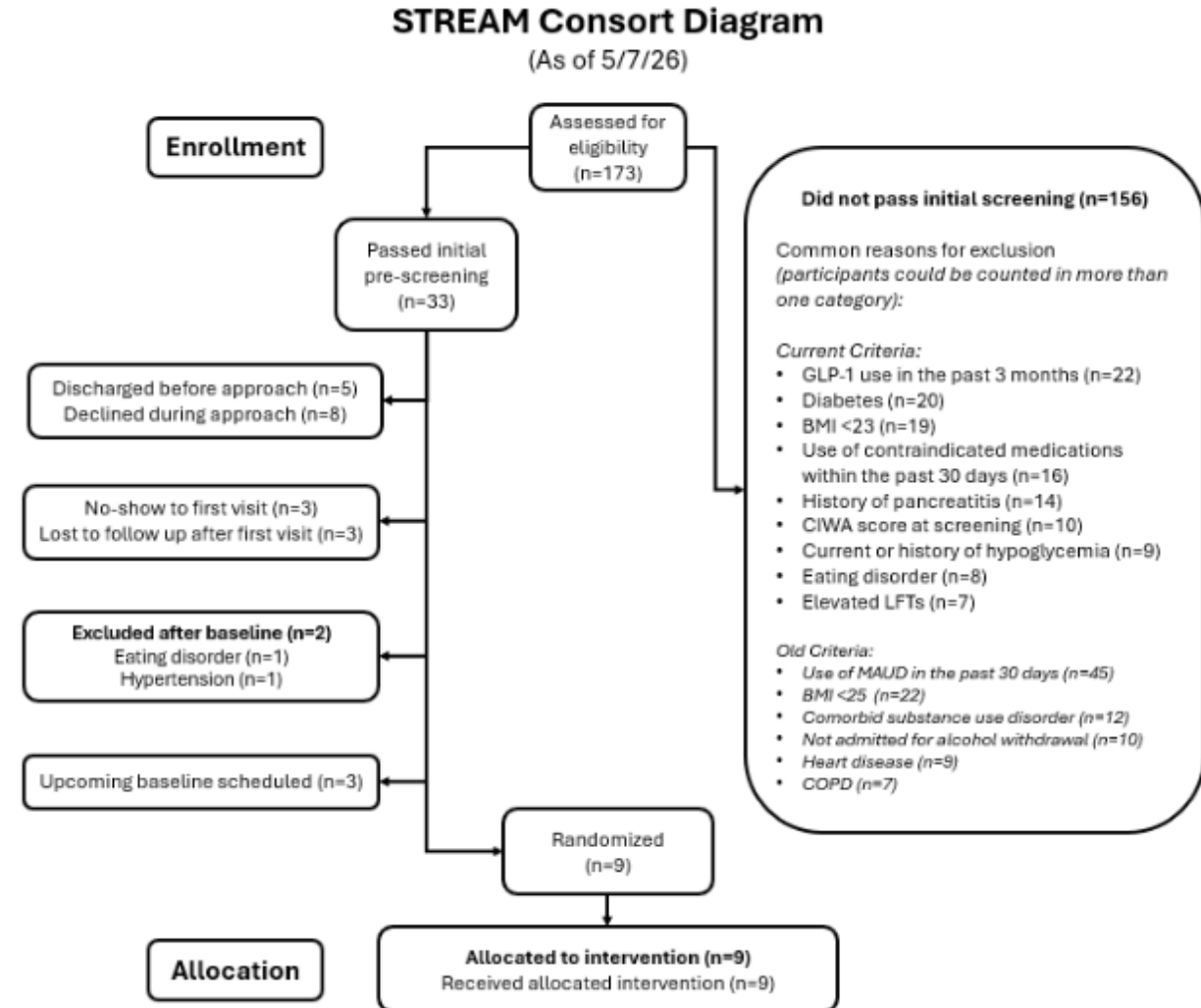
SHORE Consort Diagram
(As of 5/7/26)



Ongoing clinical trials at BWH

Tirzepatide for the treatment of AUD

- BWH-funded (McGraw Innovator Award)
- Pilot, 4-week, double-blind, placebo-controlled, randomized trial of individuals with AUD to receive either weekly injections of tirzepatide or placebo.
- Peer support offered throughout; permit MAUD
- Recruit individuals (n=20) completing inpatient withdrawal treatment
- fMRI pre and post
- **Aim 1:** Determine the effects of tirzepatide on alcohol cue-reactivity.
- **Aim 2:** Assess the safety and preliminary efficacy of tirzepatide for severe AUD



Completed, ongoing, and planned trials of GLP-1 for AUD (not a complete list!!)

Semaglutide (STAR-T)

- **Completed**
- 12-week, DBPC, RCT
- Any AUD + Overweight (n=80)

Semaglutide± Cagrilintide (Novo Nordisk)

- **Completed**
- Multi-site, DBPC, RCT
- Individuals with alcohol use and liver fibrosis (n=270)

Semaglutide (PI: Fink-Jensen)

- **Completed**
- 26-week, DBPC, RCT
- Individuals with AUD + obesity (n=108)
- MRS + fMRI

Oral Semaglutide (PI: Schact)

- **Completed**
- 8-week DBRCT
- Individuals with AUD (n=50)

Semaglutide (STAR-B)

- **Recruiting**
- 20-week, DBPC, RCT
- Any AUD (n=80)
- fMRI
- VR food choice

Semaglutide (PI: Freiberg)

- **Recruiting**
- 12-week, DBPC, RCT
- Individuals who consume alcohol and HIV (n=200)
- Tobacco use
- IL-6

Tirzepatide (PI: Hendershot)

- **Recruiting**
- 8-week, DBPC, RCT
- Individuals with AUD and obesity (n=42)
- Dose up to 5.0mg

Brenipatide (Eli Lilly)

- **Recruiting**
- Multi-site, international, Phase 3, DBPC, RCT (n=1100) of individuals with AUD

Oral semaglutide ± naltrexone (PI: Huhn)

- **Not yet recruiting**
- Single-site 2-week, DBPC, RCT (n=45) of individuals with AUD in inpatient setting
- Dose up to 7mg

Completed, ongoing, and planned trials of GLP-1 for SUD

(not a complete list!!)

Liraglutide (PI: Grigson)

- **Completed**
- DBPC, RCT (n=25) for **MOD** in MOD
- 25 enrolled, 9 completed (liraglutide =1, placebo =8)
- Results not published

Semaglutide (PI: Grigson)

- **Recruiting**
- Multi-site, 12-week, DBPC, RCT (n=200) of individuals with **MOD** on MOD
- Dose up to 1.0mg

Tirzepatide (PI: Winhusen)

- **Recruiting**
- Multi-site, NIDA CTN, DBPC, RCT (n=310) of individuals with **MOD** on SL buprenorphine

Brenipatide (Eli Lilly)

- **Recruiting**
- Multi-site, international, DBPC, RCT (n=465) of individuals with **MOD** on SL buprenorphine

Semaglutide (PI: Yamine)

- **Recruiting**
- 28-week, DBPC, RCT of **smoking** cessation and limiting weight gain (n=197)
- Dose up to 2.4mg

Semaglutide (PI: Agrawal)

- **Not yet recruiting**
- Open-label, 6-months for **smoking** cessation +NRT vs only NRT (n=100)

Semaglutide (PI: Goodman-Reza)

- **Not yet recruiting**
- 12-week, open-label, for **StUD** (n=40)
- Dose up to 1.0mg

Tirzepatide (PI: Jha)

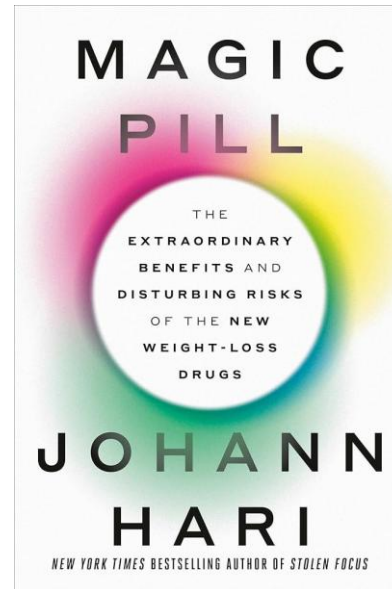
- **Active**
- 32-week, open-label (n=45) for **StUD**
- Obese or overweight with at least one co-morbid condition
- Dose up to 15.0mg

Tirzepatide (PI: Chao)

- **Recruiting**
- 52-week DBPC, RCT, for **BED** and obesity (n=105)
- Tirzepatide + placebo vs Placebo + lisdexamfetamine



12 risks of GLP-1s you need to know according to Johann Hari



Severe GI distress

Pancreatitis

Kidney injury

Gallstones

Vision changes (NAION)

Thyroid tumors

Muscle loss

Weight regain (or relapse?)

Eating disorder

Suicidal ideation (psych)

Overuse (misuse?)

Uncertain long-term effects



If weight regain happens immediately after stopping, are patients at risk of relapse?



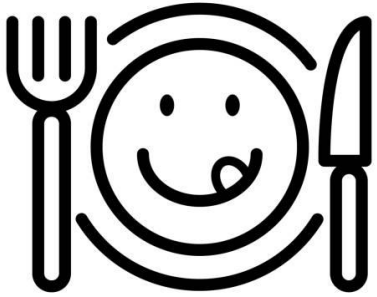
Case from a patient at BWH:

Patient X is a woman in her 60s with a past medical history of hypertension, alcohol use disorder (AUD), major depressive disorder, binge eating disorder and obesity (body mass index 30–39.9) who presented to the BWH Bridge Clinic for treatment of AUD.

Semaglutide started for obesity and binge-eating disorder, which she responded well to both. Noticed her drinking and cravings dramatically reduced.

However, lost coverage of the medication, and 2 weeks later, reported increased cravings and escalation in her drinking.

While concerns exist for emergence of disordered eating, studies so far only rarely report them, but caution is advised



Studies show disordered eating generally improves on GLP-1s...

Systematic reviews and meta-analysis pointing to improved emotional eating and only rare reports of worsening disordered eating.

(*Pierret et al 2025 JAMA Psychiatry; Jebeile et al 2025  Obesity Reviews*)



...but pharmacovigilance studies pointing to greater odds of reporting of disordered eating

FDA Adverse Event Reporting System analysis found elevated odds of eating disorders (ROR=1.57), binge eating (ROR=2.70), fear of eating (ROR=3.35), and self-induced vomiting (ROR=3.77).

“...our clinical experience warns of a need for intensive monitoring and deeper understanding, as their potent efficacy could also inadvertently lead to extreme dietary restriction and weight loss in some patients. Consequently, we stand at a critical juncture in weight loss management, calling for a well-defined strategy to approach this challenging terrain.” (**Rochards and Khalsa 2024 Obesity Reviews**)

Proactive
screening and
continuous
monitoring

Vigilant monitoring
of appetite-related
maladaptive
responses

Ongoing
assessment for
broader health
impacts

Psychiatric safety of GLP-1RAs: No increased risk of mental health adverse effects, potential benefit



Decreased depression symptoms

A meta-analysis of 5 RCTs and 1 prospective study (n=2,071) targeting DM2 with GLP-1s found improved depression scores vs placebo
(*Chen et al 2024 Am J Geriatric Psych*)



No increase in psychiatric adverse effects, improvement in emotional eating and QOL

A meta-analysis (80 RCTs, n=107,860 and 31 RCTs, n=84,713) of obese/diabetic patients on GLP-1s vs placebos showed no elevated risk of suicidality, depression, or new-onset psychiatric illness. Improvement in emotional eating and quality of life
(*Pierret et al 2025 JAMA Psychiatry*; *Silverii et al 2024 Diabetes Obes Metab*)



Safe in psychiatric patients on psychotropics

Systematic review of 36 studies that enrolled obese/diabetic patients with and without co-morbid psychiatric disorders on antipsychotics or antidepressants found no worsening of mental health outcomes
(*Breit & Hubl 2025 Psychoneuroendocrinology*)

Drug-Drug Interactions between GLP-1 and oral medications are raising safety concerns due to alterations in PK



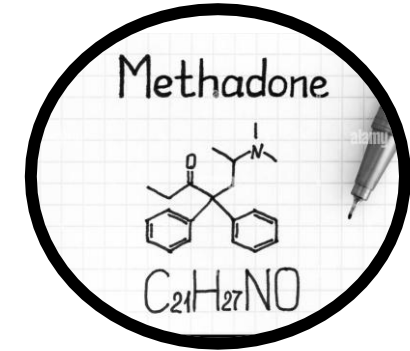
Emerging evidence points to altered PK

Systematic review identified that GLP-1 sometimes reduced C_{max} and delayed T_{max} , but typically no clinically significant change in AUC. However, medications with narrow therapeutic index like anticoagulants may require closer monitoring
(*Calvarysky et al 2024 Drug Safety*)



Case reports of lithium toxicity after initiating GLP-1

Case reports of patients with bipolar disorder on lithium who experienced significant rise in lithium levels after initiating GLP-1. Potential mechanisms include dehydration, altered kidney function, and delayed gastric emptying
(*Al-Soletti et al J Clin Psychopharmacol*)



No data on whether GLP-1s will affect PK of methadone

C_{max} , not just AUC, may be an important determinant of suppression of cravings, withdrawal, and countering respiratory depressing effects of methadone. Those on stable MMT dose may or may not require closer monitoring or dose adjustments.

Athletes already using GLP-1s, prevalence unknown, and unclear if they are performance enhancing drugs



Rapidly emerging “micro-dosing” market for GLP-1RAs without any empirical support for their efficacy

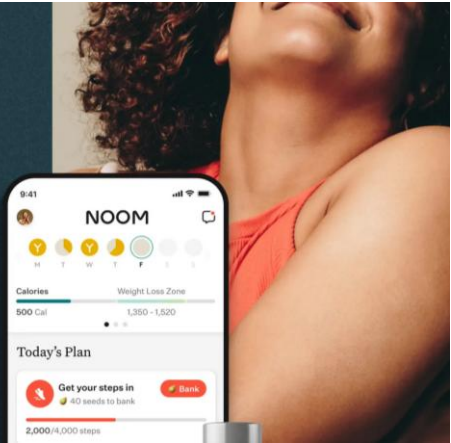
FDA & HSA ELIGIBLE

Microdose: the easiest way to start a GLP-1

Noom Microdose GLP-1^{rx} Program helps you lose weight on the lowest effective dose.

- Affordable – plans start at \$119!
- Minimal side effects – more than 70% of members experience none at all!
- Paired with behavior change and coaching – for results that last

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Ease into weight loss

Lose weight and get support managing side effects with Compounded GLP-1 Microdose treatment plans.





Forbes HEALTH

Best GLP1 For Microdosing Of 2026

Below are several of the most popular telehealth platforms for obtaining prescription weight loss medications online. Choose the best fit for your goals and lifestyle.

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- 100% online prescriptions with fast & free shipping

9.8

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- Access to the Wegovy pill (first and only FDA-approved GLP-1 weight loss pill), if prescribed
- Access to the fastest working GLP-1 for half the list price
- Get started online for just \$45

9.8

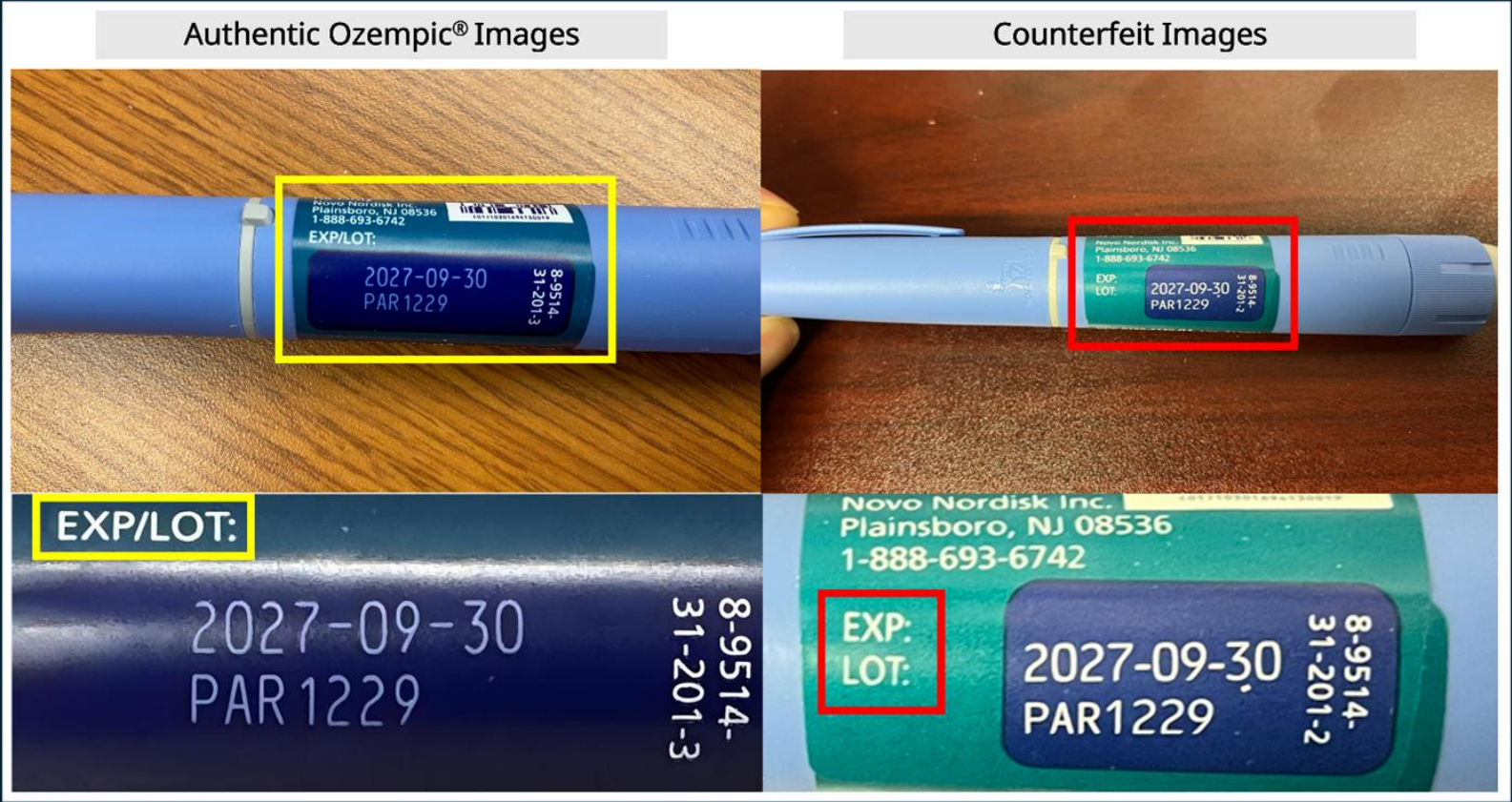
EXCELLENT

★★★★★

Visit Site →

Go to Ro

FDA has been raising alarms for several years for the unapproved use of GLP-1 and counterfeit supply



FDA Dec 2025: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain>

Should we be recommending GLP-1s to patients with SUD?



- Reasonable for those with indications for GLP-1
- But efficacy not yet established!!
- We should be **FIRST** maximizing the use of existing treatment options including FDA-approved treatments

Conclusions

- **GLP-1RAs offer a novel therapeutic avenue for SUDs** by modulating brain circuits involved in reward processing and energy balance
- **Modulate the “wanting”, “liking” and promote feeling “satiated”**, providing new ways to think about SUD treatment targets
- **Early clinical trials show promise in AUD**—with additional trials underway for multiple SUDs
- **Demonstrated psychiatric safety** supports their use in patients with mental illness, particularly those taking psychotropic medications, but caution advised for the possibility of disordered eating and PK alterations.



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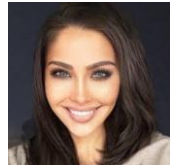


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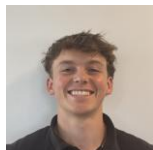


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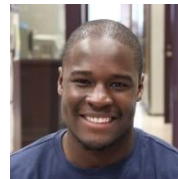


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