



Injecting Hope: GLP-1 receptor agonists for the treatment of substance use disorders

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Disclosures

- I receive:
 - NIH funding to conduct clinical trials including for semaglutide for OUD (R21DA060304).
 - In-kind support from Braeburn to use Brixadi to conduct a NIH-funded trial (R21DA060411).
 - Research support from Eli Lilly for a clinical trial of GLP-1 to treat opioid use disorder (NCT07420283)
- I have no other relevant financial conflicts of interest to disclose.



Learning Objectives

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

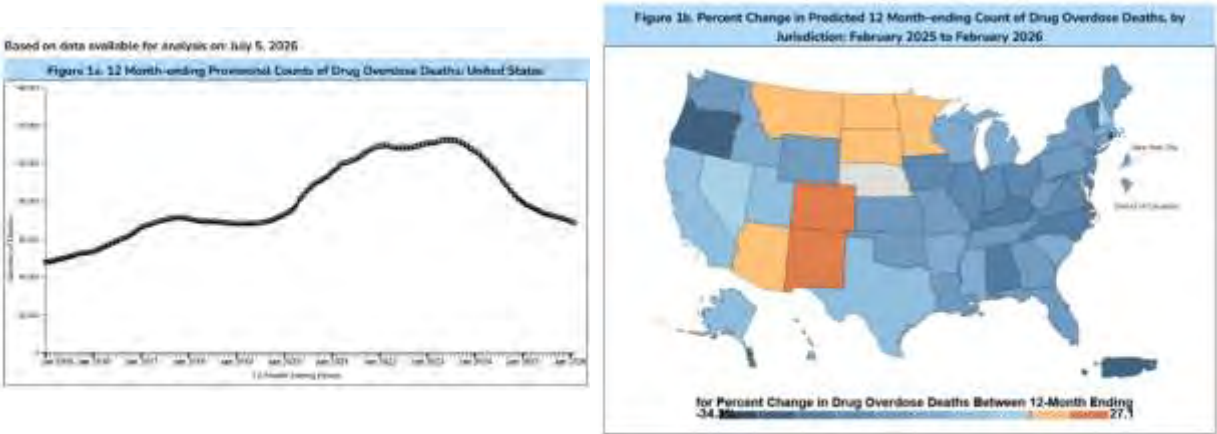
- 1. Describe the pharmacology of GLP-1 receptor agonists
- 2. Evaluate the emerging evidence base to support their use in treating substance use disorders
- 3. Outline concerns being raised surrounding the use of GLP1s for SUD



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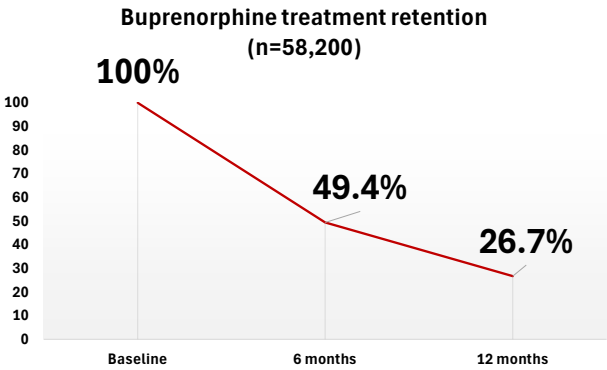
Drug overdose deaths in the US are declining, but numbers remain high



CDC 2026 4

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



Sordo et al BMJ 2017; Xu et al Addiction Sci Clin Practice 2024

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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

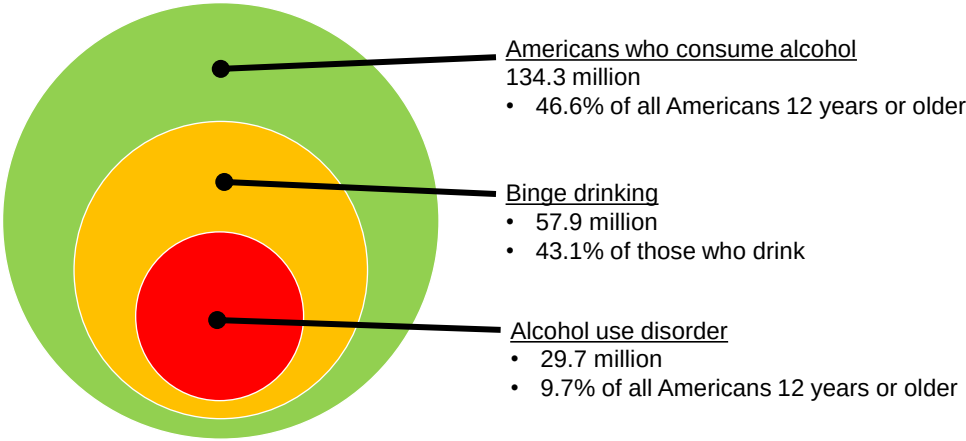


Volkow and Blanco 2023 American Journal of Psychiatry

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Unhealthy alcohol use remains common in the US



NSDUH 2025 ⁷

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

Naltrexone PO	Naltrexone IM	Acamprosate	Disulfiram
Initiate at 50mg daily, can consider higher doses if indicated	Ideally prior PO trial, but not absolute	666mg TID but dosing flexible (i.e. 999mg BID)	Limited to those with higher motivation for abstinence
AE: dizziness, somnolence, GI distress, fatigue	AE: Liver toxicity even less likely; injection site reaction	AE: GI distress	Particularly effective if incorporate significant other
Contraindications: Need for opioids, decompensated liver cirrhosis (Child Pugh C)	Hospital initiation may be covered by manufacturer	Contraindicated in renal impairment (CrCl<30)	AE: liver toxicity, psychiatric AE at higher doses, GI distress, fatigue, (Child Pugh B/C)



Han et al 2021 JAMA Psychiatry ⁸

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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



NIAAA 2024 9

The **Suzuki Lab** at the Brigham aims to rigorously test novel treatments for substance use disorders.

Four Key Areas of Research



Research to treat substance use disorders in the hospital and emergency room



Buprenorphine-related studies (e.g. low-dose inductions, dental complications)



GLP-1 medications targeting alcohol and opioid use disorders



Psychedelics as treatments for alcohol and opioid use disorders



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



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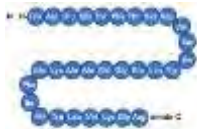
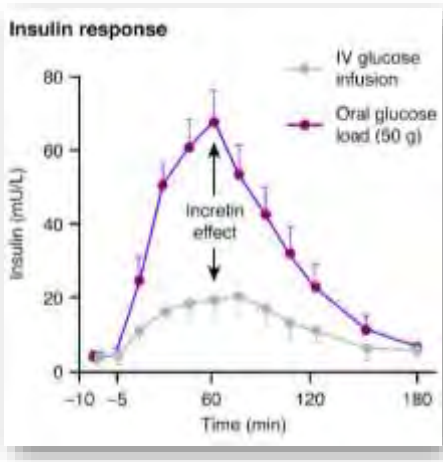
GLP-1 was one of the first incretins to be discovered

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

Glucose-dependent insulintropic polypeptide (GIP)



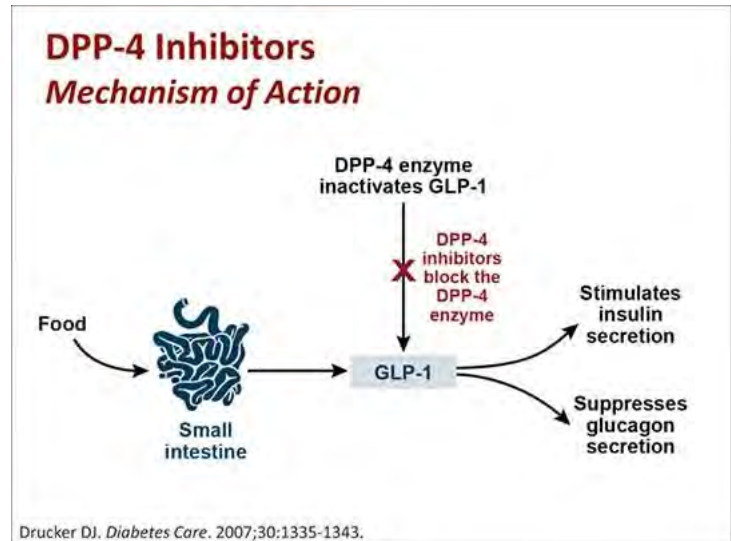
Glucagon-Like Peptide-1 (GLP-1)



Ahluwalia and Vora 2012 Bri J Diabetes & Vascular Dis¹²

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- 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.

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

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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.

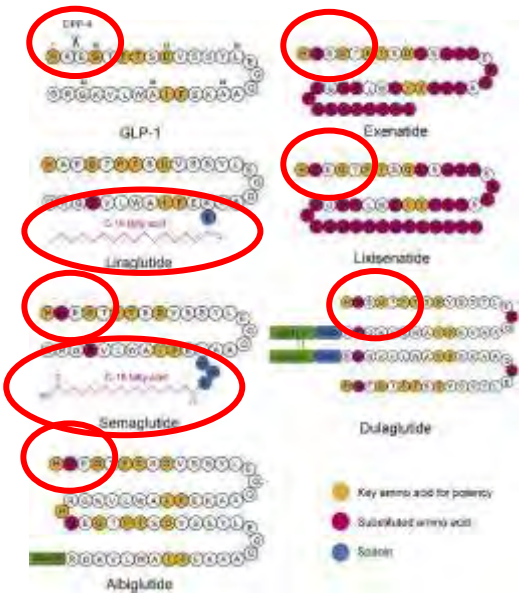
In humans, exendin-4 had a half-life about 2.4 hours, almost 100 times longer than the native GLP-1!



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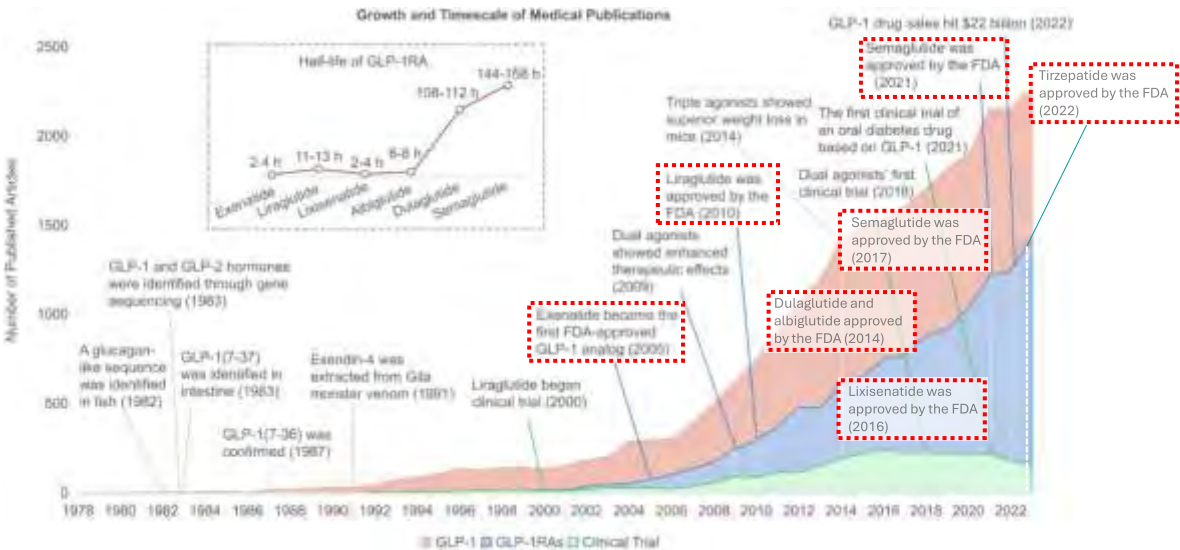
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Subsequent research focused on increasing half-life by resisting degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), and enhancing binding to the GLP-1 receptor.



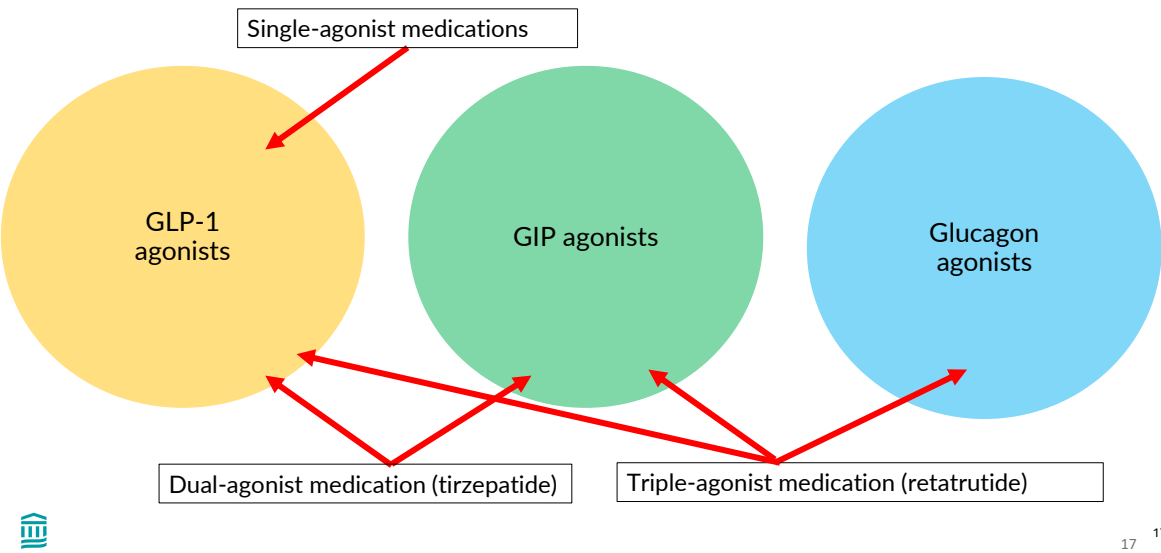
Yu et al 2018 Advanced Drug Delivery Reviews

Growth and Timescale of Publications on GLP-1RAs



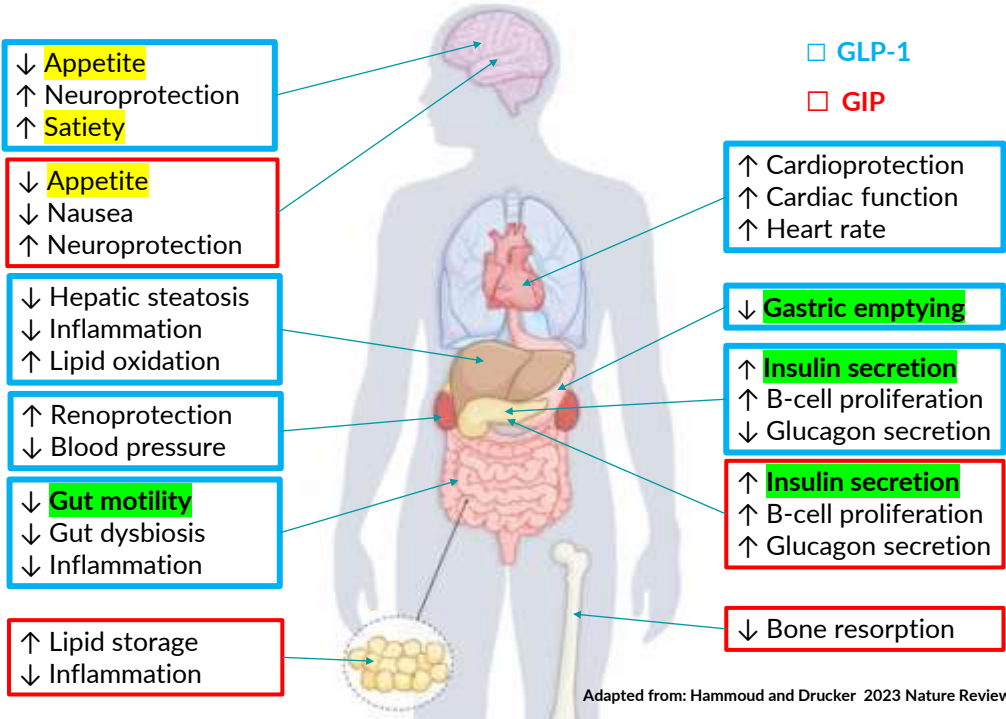
Adapted from Zheng et al 2024 Signal transduction and targeted therapy

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



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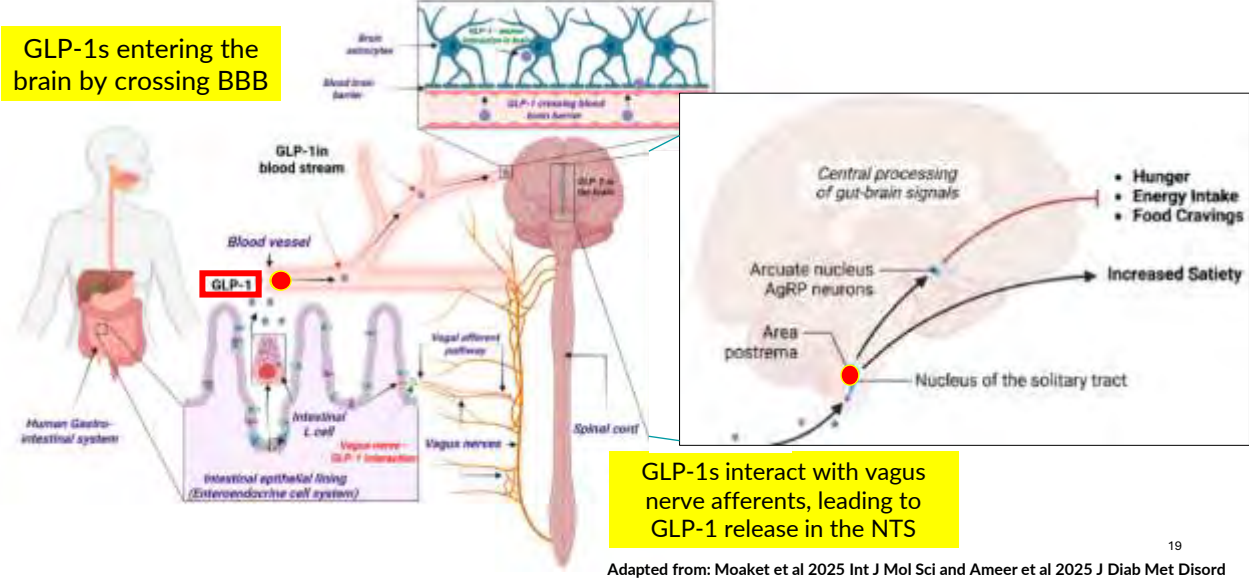
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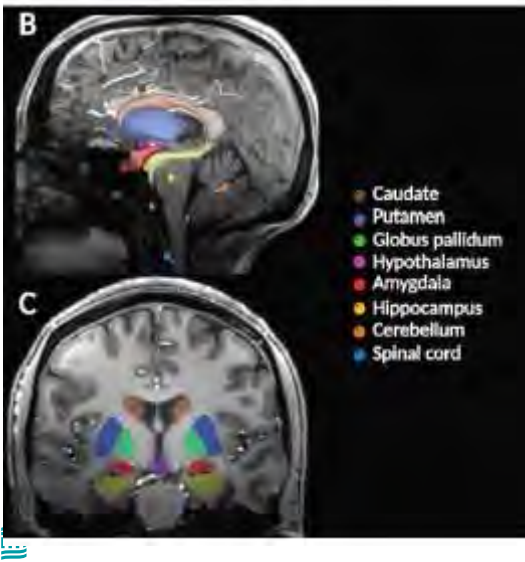
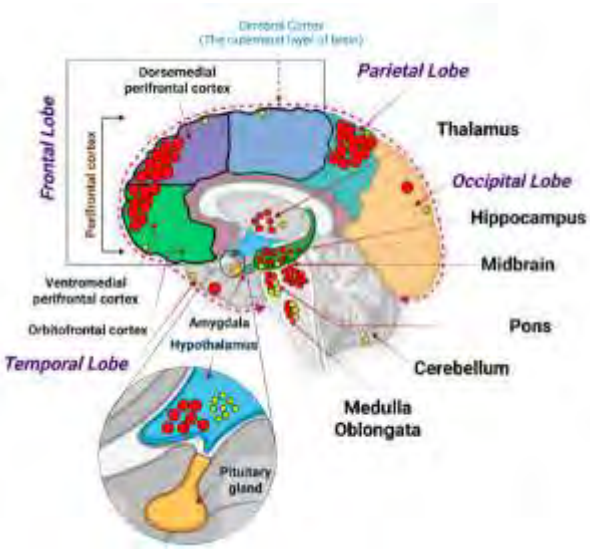
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Peripherally released GLP-1s access the brain directly and indirectly, but the brain produces its own GLP-1s in the NTS

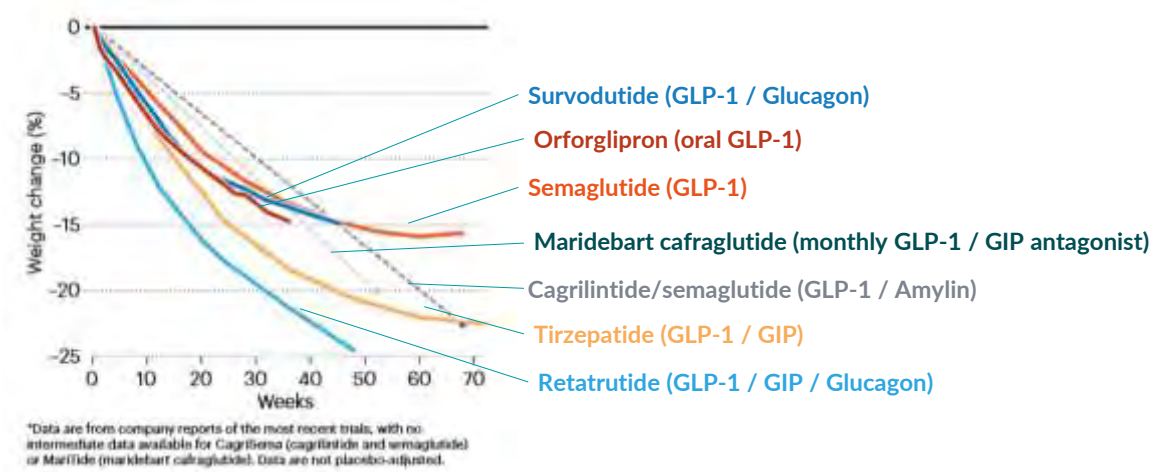


GLP-1 receptors are widely found in the brain, particularly in the reward-related regions.



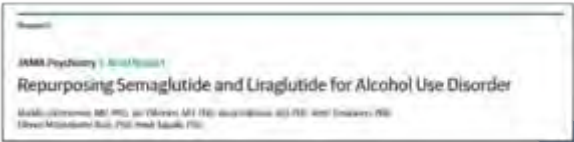
Lopez-Ojeda and Hurley 2024 J Neuropsych Clin Neurosci; Moaket et al 2025 Int J Mol Sci

Next-generation obesity drugs are arriving soon



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Dolgin 2025 Nature

Epidemiologic evidence in support of GLP-1 RAs in addressing alcohol use



Objective: To test whether risk of hospitalization from AUD is decreased with GLP1

Design: Retrospective cohort of all Swedish residents with AUD using nationwide Swedish data from 2006 to 2023.

Exposure:

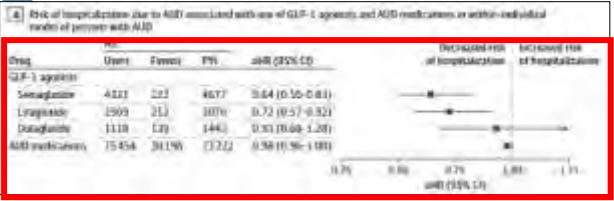
- Use of GLP-1 vs non-use of GLP-1
- Use of MAUD medications

Outcomes:

- AUD-related hospitalization

Results:

- 227,866 individuals with AUD
- 133,210 (58.5%) with AUD hospitalization
 - Semaglutide (n=4321) with lowest risk (aHR 0.64)
 - Liraglutide (n=2509) with next lowest risk (aHR 0.72)
 - Any MAUD with modest decrease (aHR 0.98)



Conclusions:

- GLP1s, especially semaglutide, associated with >30% reduction in AUD-related hospitalization



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SOURCE: Lahteenvuio et al JAMA 2024

Epidemiologic evidence in support of GLP-1 RAs in addressing alcohol use



Objective:

- Evaluate the association between the use of semaglutide for obesity/T2D and incident and recurrent AUD

Design

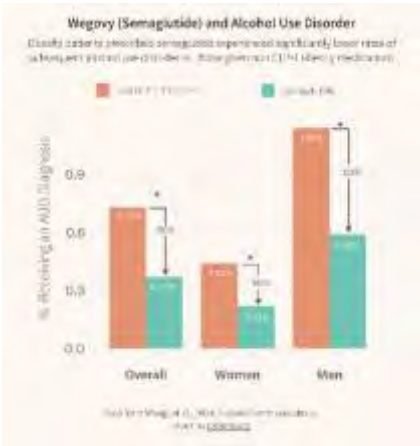
- Retrospective cohort study using the TriNetX network (EHR from 105million patients in the US)
- Patients with obesity or T2D with or without AUD
- Prescribed semaglutide or other non-GLP-1RA anti-obesity medications including naltrexone and topiramate from June 2021 to December 2022
- Propensity score matched

Outcome

- Assess for incident and recurrent AUD

Results:

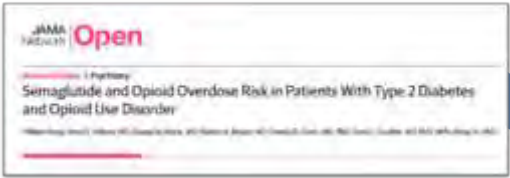
- Semaglutide associated with a 50–56% lower risk of both incident and recurrent AUD diagnoses over 12 months compared to other anti-obesity or anti-diabetes medications.



Conclusions: Results point to a potential benefit of semaglutide for AUD in those with obesity of diabetes

SOURCE: Wang et al 2024 Nature Communications; <https://recursivadaptation.com/p/the-growing-scientific-case-for-using>

Epidemiologic evidence in support of GLP-1 RAs in addressing opioid use



Objective: To examine if semaglutide prescribed for individuals with diabetes and OUD have impact on overdose risk

Design: Emulation target trial to compare association of semaglutide vs other antidiabetic medications (i.e. insulin, DPP-4s, SGLT2is, other GLP1RAs) with opioid overdose risk among patients with diabetes and OUD. Includes de-identified data of 116.6 million patients in the US. Propensity score matching for insulin, and follow-up for 12 months .

Exposure:

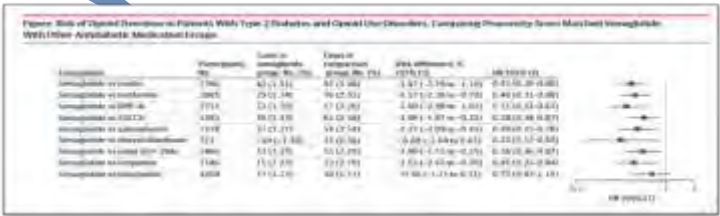
- Semaglutide vs other antidiabetic medications between 2017 and 2023.

Outcomes:

- Opioid overdose

Results:

- 33,006 eligible individuals:
 - 3,034 prescribed semaglutide (Mean age 57.4, 56.5% female)
 - 29,972 prescribed other medications
- Semaglutide associated with significantly lower risk of OD (HR 0.32 to 0.58)

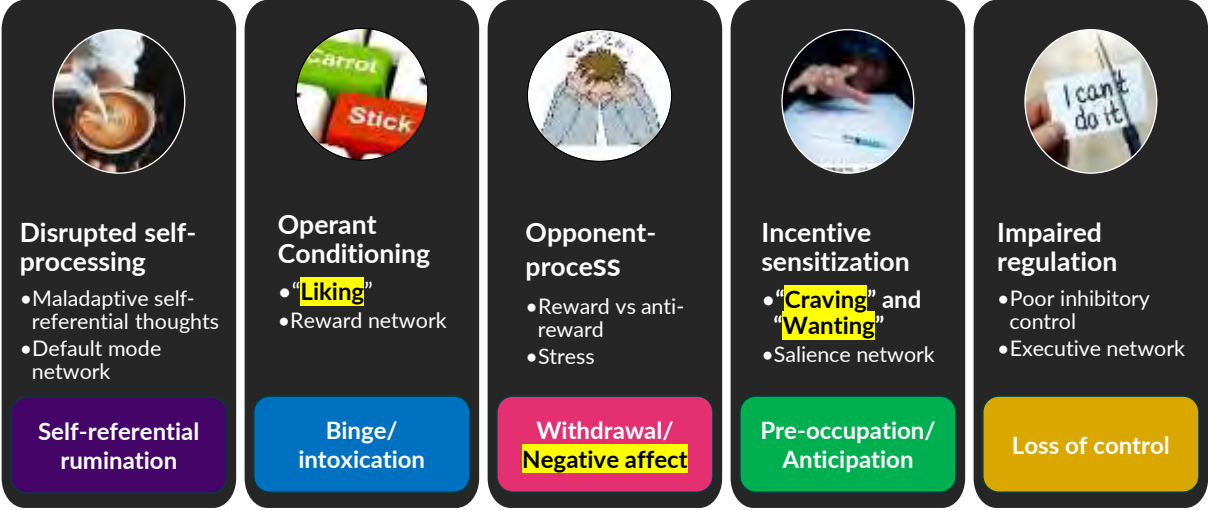


Conclusions:

- Semaglutide associated lower risk of opioid overdose compared to other medications for diabetes as well as other GLP1s (except dulaglutide).

SOURCE: Wang et al JAMA 2024

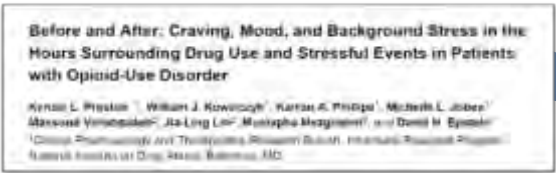
Neurobiological model of substance use disorders



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Cravings and stress/negative affect are elevated prior to relapse



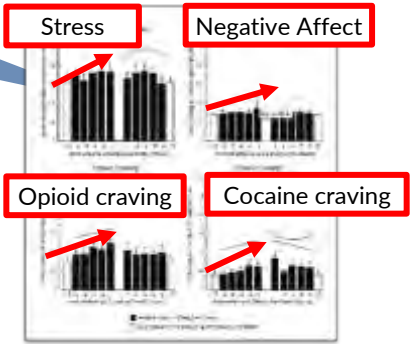
Setting: Outpatient treatment center in Baltimore

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



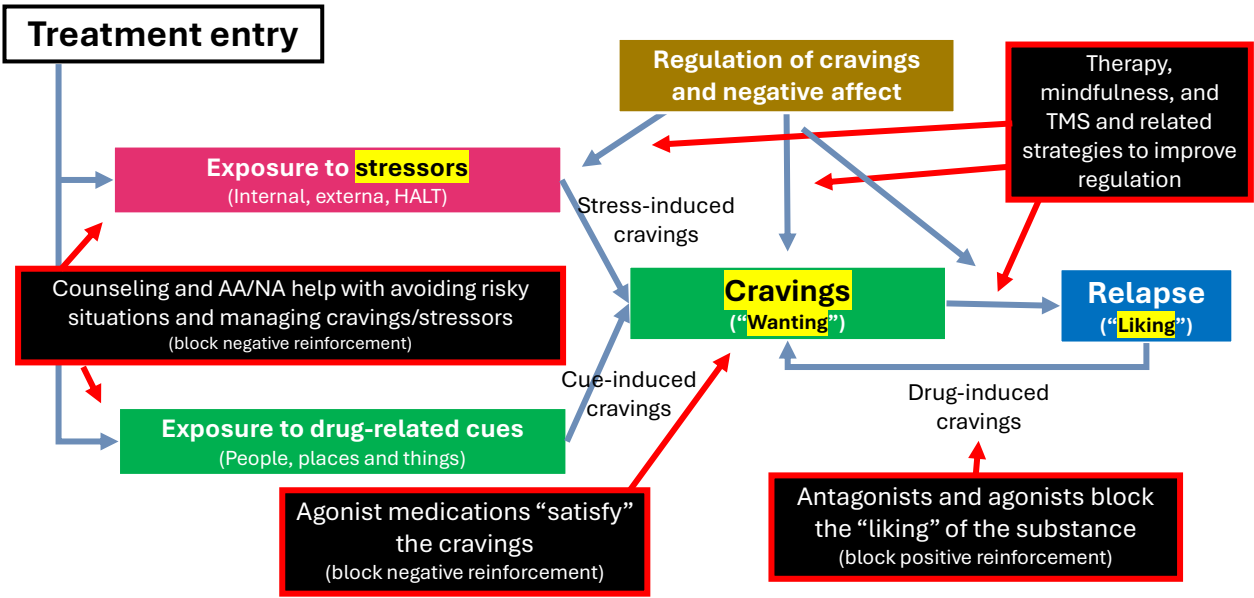
Conclusion: Stress, cravings, and negative mood are increasing prior to use events



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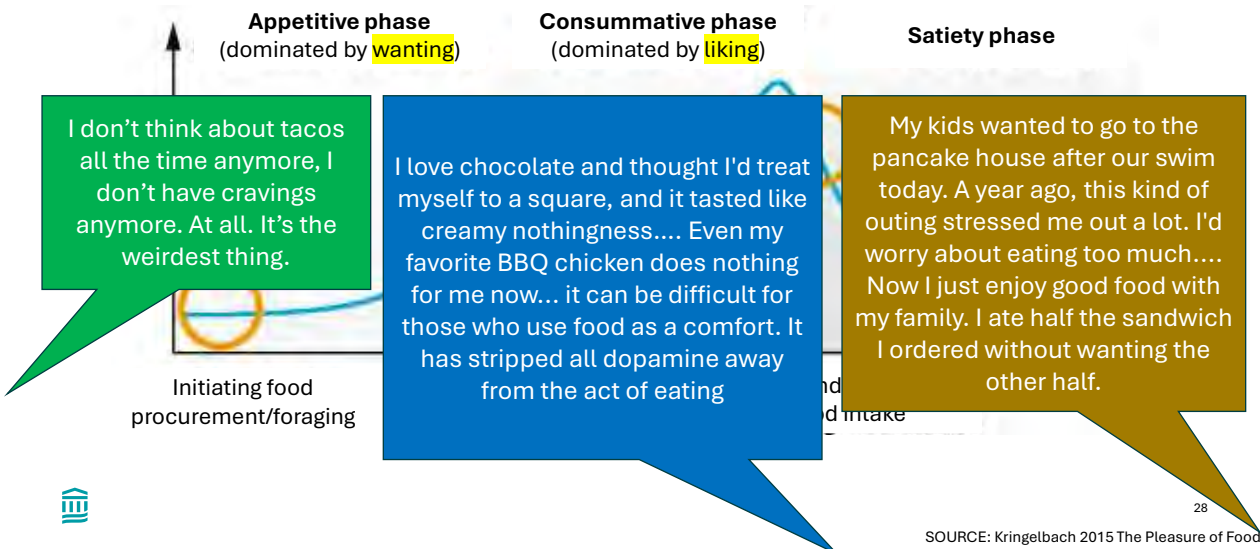
SOURCE: Preston et al Psychopharmacology 2018

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



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"One of the things that I realized the very first time I took a GLP-1 was that all these years I thought that thin people just had more willpower, they ate better foods, they were able to stick to it longer, they never had a potato chip, and then I realized the very first time I took the GLP-1 that, 'Oh, they're not even thinking about it. They're only eating when they're hungry, and they're stopping when they're full.... It **quiets the food noise.**"

–Oprah



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Anecdotal reports that GLP-1s help reduce substance use

"I remember going to dinner for the first time [while taking Ozempic]... I ordered a beer, took a sip, and I couldn't finish it.... You know how sometimes you taste a beer, and it's like, 'Oh my God, this tastes so good that I want to guzzle it.' Well, I didn't feel like guzzling. **I just really felt like sipping it.**"



"Before Ozempic, I could consume a whole bottle of wine in an evening without trying real hard, along with a bag of chocolates.... But with Ozempic, even one beer **didn't feel good** to me somehow... **I had no idea this would happen**... Nobody told me anything about the drug affecting alcohol, too."



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



- 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:
- Trials mostly negative
 - GLP1s might benefit substance use, but only if overweight?
 - Further research warranted

Shen et al Journal of Addiction Medicine 2024



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



- 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.



Hendershot et al JAMA Psychiatry 2025



Positive results for semaglutide for AUD in second RCT

Table. Pretreatment Characteristics by Treatment Group for All Randomized Participants

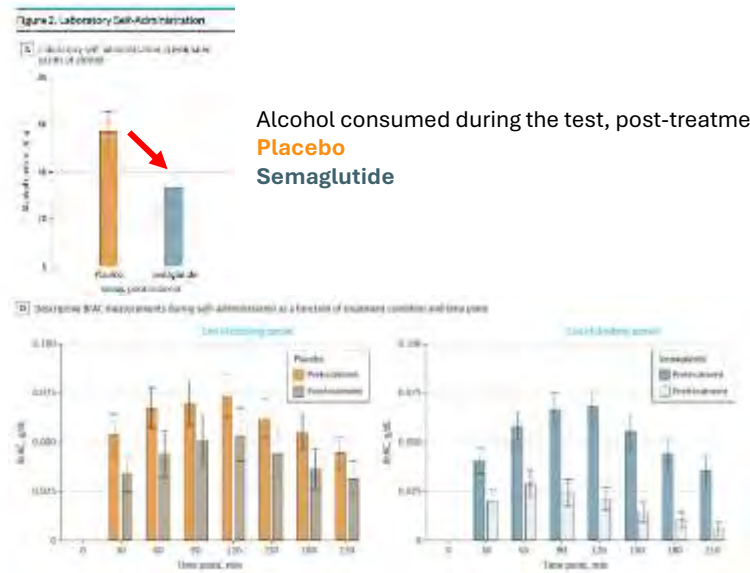
Characteristic	Placebo	Semaglutide	Total
Randomized, No.	24	24	48
Sex, No. (%)			
Female	17 (71)	17 (71)	34 (71)
Male	7 (29)	7 (29)	14 (29)
Age, y	39.0 (10.9)	40.6 (10.5)	39.9 (10.6)
Race, No. (%) ^a			
Asian	2 (8)	0	2 (4)
Black/African American	4 (17)	3 (13)	7 (15)
Hawaiian/Pacific Islander	0	0	0
White	18 (75)	21 (88)	39 (81)
Alcohol consumption ^b			
Drinks/calendar day	3.0 (3.7)	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, RACS 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

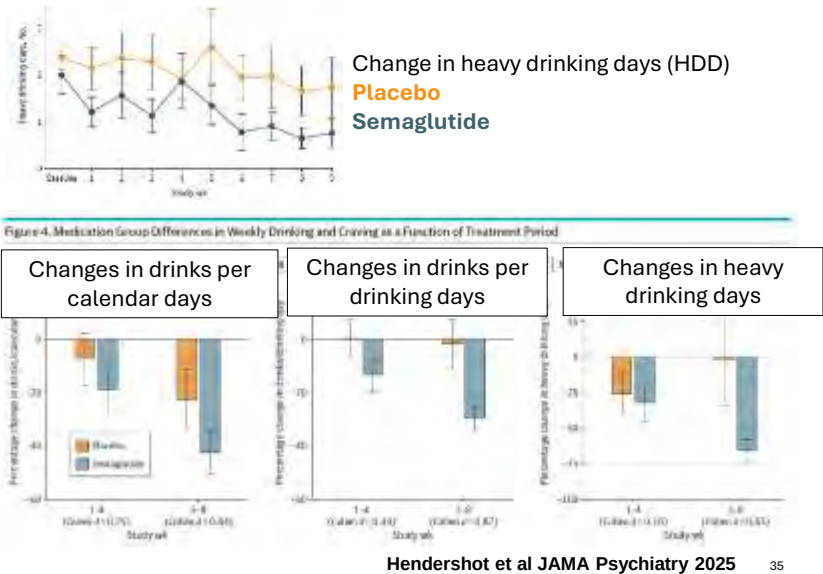
Results:

- Significant reduction in laboratory self-administration task



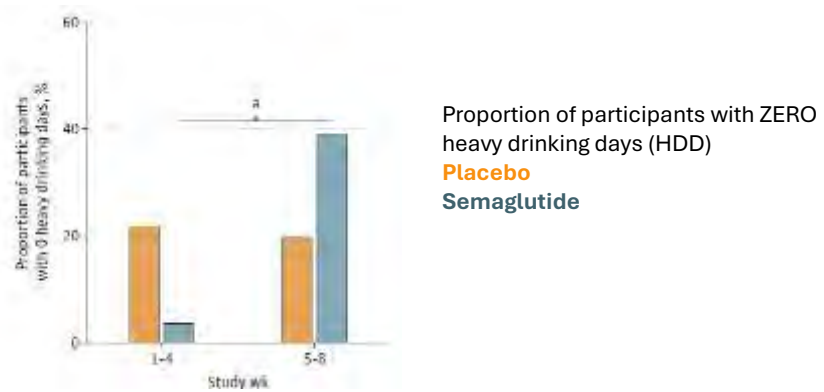
Positive results for semaglutide for AUD in second RCT

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



Positive results for semaglutide for AUD in second RCT

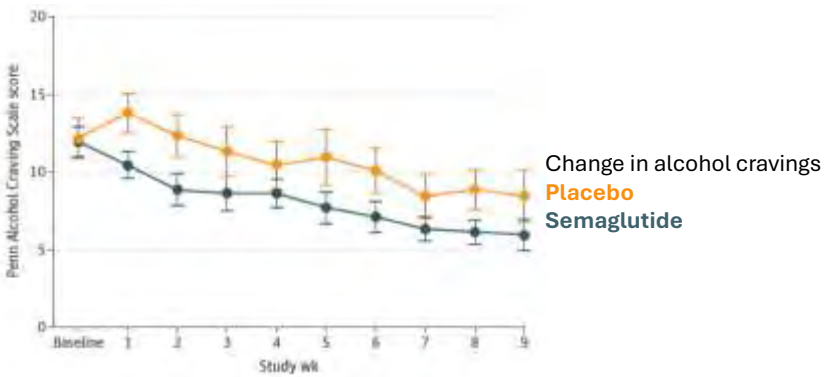
- Results:
- Overall, **significant reduction in HDD** compared to placebo, but reduced **drinks per drinking day and alcohol cravings**



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**



Hendershot et al JAMA Psychiatry 2025 37

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

Walter R, et al. Lancet. 2026;401(10388):10388-10398. doi:10.1016/S0140-6736(25)01038-8. Epub 2025 Oct 30. PMID: 41811111.

- 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)

Klausen et al Lancet 2026

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

	Placebo (n=54)	Semaglutide (n=54)		Placebo (n=54)	Semaglutide (n=54)		Placebo (n=54)	Semaglutide (n=54)
Sex assigned at birth*			Previous pharmacological treatment for alcohol use disorder			Drinking days (percentage points)		
Male	28 (52%)	27 (50%)	Disulfiram	5 (17%)	10 (19%)	Heavy drinking days†	12.2 (7.4)	12.1 (6.2)
Female	26 (48%)	27 (50%)	Acamprosate	5 (9%)	5 (9%)	6-13 days*	15 (28%)	12 (23%)
Age			Naltrexone	3 (2%)	2 (7%)	14-17 days*	14 (26%)	14 (26%)
Mean age, years	51.7 (9.8)	51.8 (9.8)	Nalmefene	0	0	18-23 days*	10 (19%)	7 (12%)
30 years and younger†	6 (11%)	5 (9%)				24-30 days*	11 (20%)	16 (30%)
Older than 40 years*	48 (89%)	49 (91%)	Alcohol use disorders identification score†			Days without alcohol consumption	8.2 (2.3)	8.7 (2.3)
Ever abstinent or treated	29 (54%)	22 (41%)	Alcohol use disorders identification consumption score†			Total alcohol consumption (g of alcohol on 30 days)	2746.5 (1055.0)	2155.3 (1121.5)
Race or ethnicity			10-15 alcohol dependence			Phosphatidyl ethanol, μmol/L	9.7 (0.4)	9.5 (0.5)
Asian	0	4 (7%)	3 symptoms			With risk drinking level		
Black or African American	4 (7%)	4 (7%)	4 symptoms			Low	3 (10%)	1 (10%)
White	33 (58%)	49 (91%)	5 symptoms			Medium	12 (22.0%)	16 (29.6%)
Hispanic	10 (19%)	10 (19%)	6 symptoms			High	23 (42.0%)	19 (35.2%)
Education			Diagnostic and Statistical Manual alcohol use disorder			Very high	39 (73.1%)	28 (51.3%)
Lower secondary school	3 (6%)	3 (6%)	Mild (2-3 symptoms)	0	0	Euglycemia test for fasting Dependence score‡	4.5 (2.8)	3.3 (2.5)
Upper secondary school	3 (4%)	2 (4%)	Moderate (4-5 symptoms)	11 (21%)	5 (9%)	Cigarettes per day	14.9 (30.5)	13.2 (9.5)
Vocational education or short-cycle higher education	71 (38%)	54 (29%)	Severe (≥5 symptoms)	43 (80%)	49 (91%)	Bodyweight, kg	88.2 (15.5)	88.3 (14.0)
Medium-cycle higher education or higher education	26 (52%)	35 (65%)				BMI, kg/m²	35.2 (4.4)	33.7 (3.8)
Previous treatment with a glucagon-like peptide-1	8 (13%)	5 (9%)				Glucated haemoglobin**	5.4 (0.4)	5.5 (0.3)

Approximately 5 drinks per day

Approximately 300-500ng/ml PEth



Klausen et al Lancet 2026

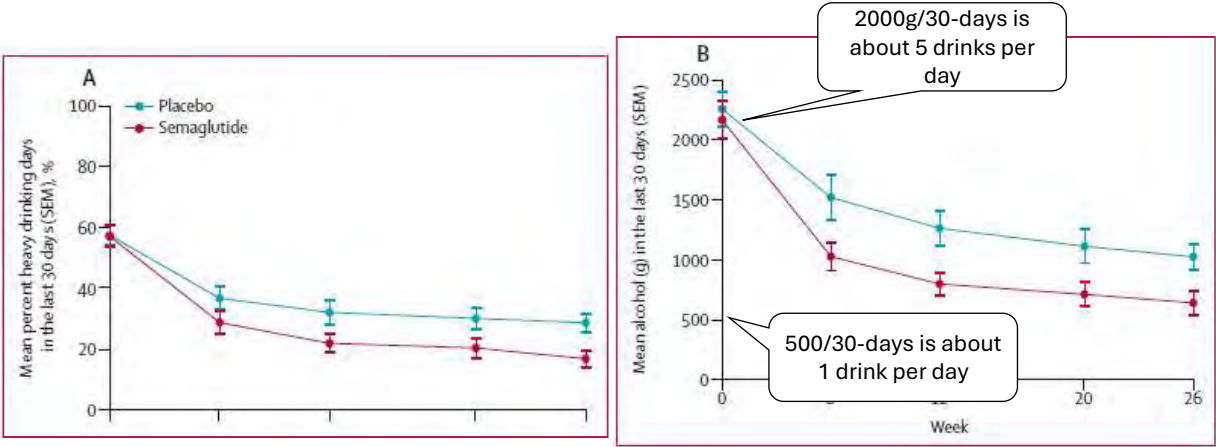
Second RCT of semaglutide for AUD... first to enroll treatment seekers

	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 (-49.7 to -32.5)	-14.7 (-22.0 to -5.4)	0.0015
Total alcohol consumption, g/30 days†	-1025.9 (-1260.0 to -791.7)	-1550.2 (-1858.2 to -1242.1)	-467.5 (-729.5 to -195.4)	<0.0009
Days without alcohol consumption, percentage points†	27.6 (19.8-35.5)	36.9 (30.6-47.3)	10.1 (-0.0 to 20.2)	0.053
Change in drinks per drinking day*	-2.3 (-3.3 to -1.3)	-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 -7.5)	-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)	-4.7 (-5.0 to -3.5)	-2.5 (-3.6 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 (-23.2 to -1.9)	-3.3 (-11.0 to 4.4)	0.40
γ-glutamyl transaminase, U/L	-10.2 (-17.5 to -2.9)	-36.0 (-52.7 to -19.7)	-24.7 (-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
FBG-4	0.0 (-0.1 to 0.1)	-1.1 (-1.2 to -1.0)	0.0 (-0.1 to 0.2)	0.67



Klausen et al Lancet 2026

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**



Klausen et al Lancet 2026

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Third RCT of semaglutide for AUD using the oral formulation

Oral Semaglutide for Alcohol Use Disorder: A Randomized Clinical Trial

Joseph P. Schacht, PhD,^{1,2,3} Joseph T. Salas, MD,¹ Kristen Raymond, BA,¹ Robert Shelton, MS,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 (≥5/≥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 → 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



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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
Maximum drinking goal	3	12	4	17	7	14
Cigarette smoker	2	8	4	17	7	14
Cannabis user (past year)	7	27	10	42	17	34
	Mean	SD	Mean	SD	Mean	SD
Age (years)	55.0	10.4	48.8	8.8	51.1	10.2
OSAS-5 AUD criteria	6.6	2.1	7.7	2.0	7.1	2.1
Alcohol consumption						
Drinks per calendar day	6.6	3.6	6.3	3.6	6.4	3.6
Drinks per drinking day	11.2	3.3	8.0	3.6	7.6	3.1
Intoxicated days per week	8.4	10.6	5.7	1.6	6.1	4.4
Heavy drinking days per week	5.4	1.7	4.5	1.6	5.0	1.6
Body mass index	32.2	5.1	30.7	3.2	31.4	4.0
Liver function tests (U/L)						
Aspartate aminotransferase	34.7	9.0	25.6	11.2	25.1	10.5
Alanine aminotransferase	26.6	13.1	27.3	19.6	26.9	16.4

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

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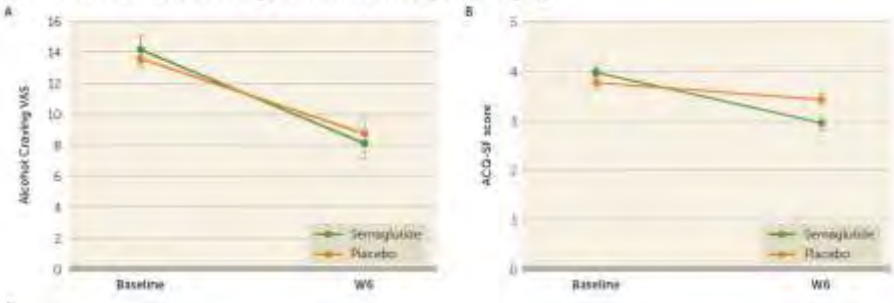
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Third RCT of semaglutide for AUD using the oral formulation

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



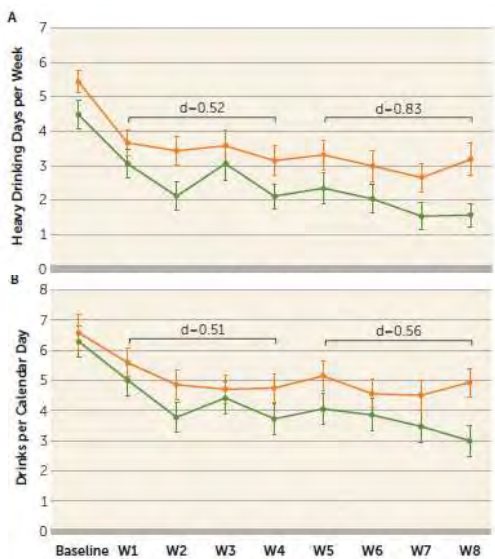
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Third RCT of semaglutide for AUD using the oral formulation

Results:

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



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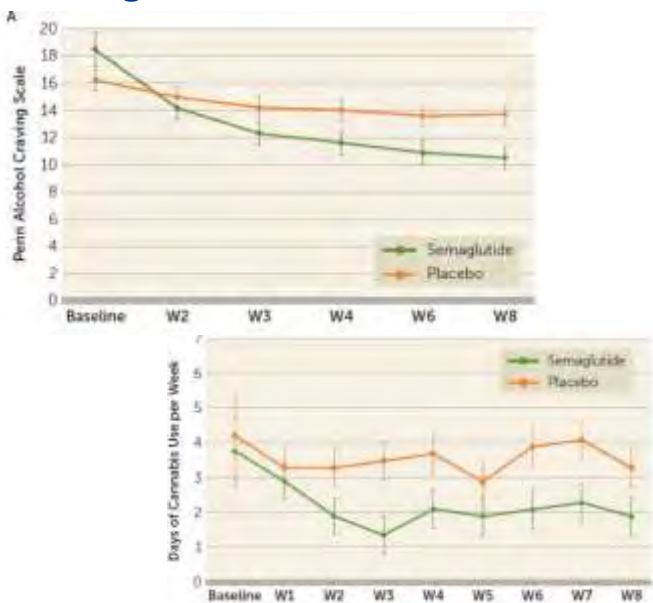
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Third RCT of semaglutide for AUD using the oral formulation

Results:

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



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

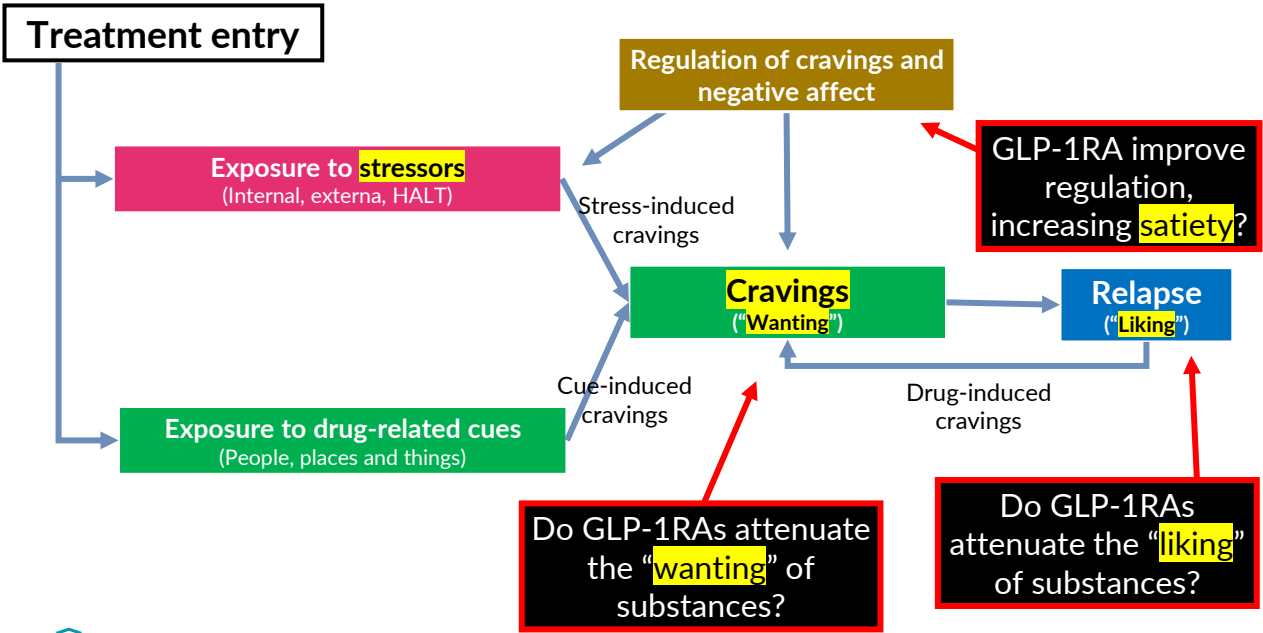
- Overall semaglutide well tolerated in all trials
- Adds to the growing body of evidence that GLP-1s will be effective treatments for AUD
- However, unclear generalizability due to:
 - ✓ Hendershot trial enrolled those who were NOT treatment seeking
 - ✓ Both Klausen and Schact trials enrolled those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



Klausen et al Lancet 2026

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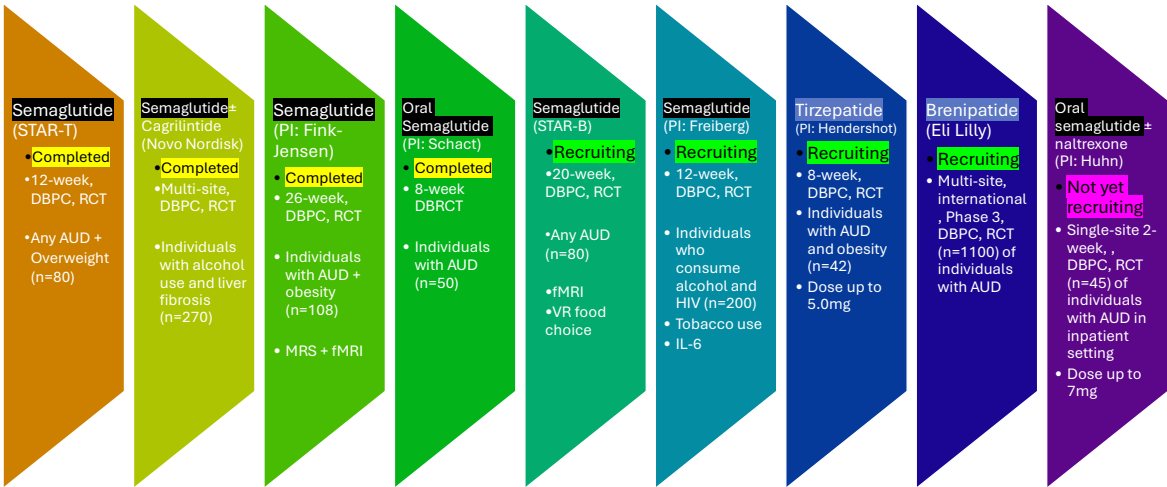
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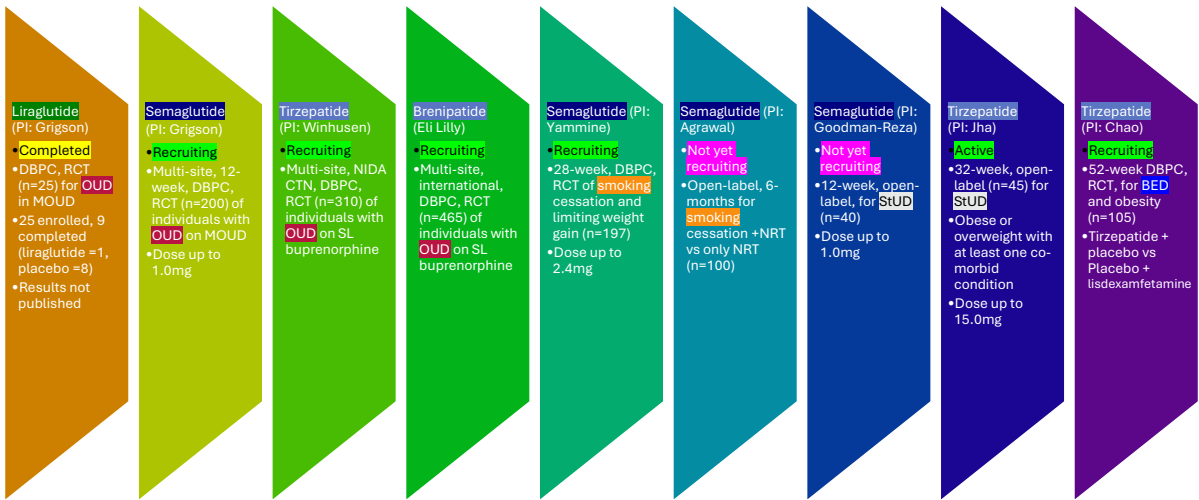
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Completed, ongoing, and planned trials of GLP-1
for AUD (not a complete list!!)



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

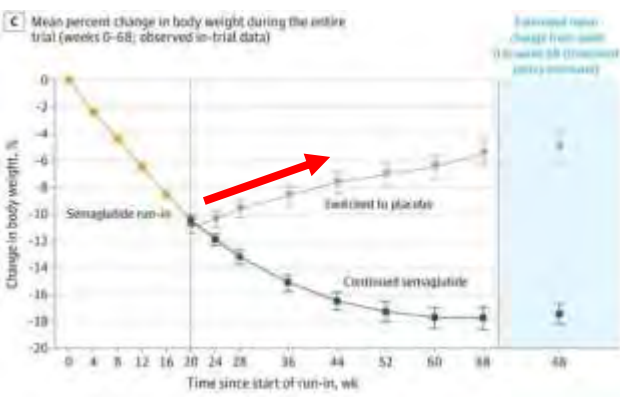


12 risks of GLP-1s you need to know according to Johann Hari



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, non-medical use, aberrant use?)	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). (Chen et al 2023 Frontiers in Endocrinology)

“...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.” (Richards and Khalsa 2024 Obesity Reviews)

Proactive screening and continuous monitoring

Vigilant monitoring of appetite-related maladaptive responses

Ongoing assessment for broader health impacts

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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-analyses (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)

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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-Soleiti 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.



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



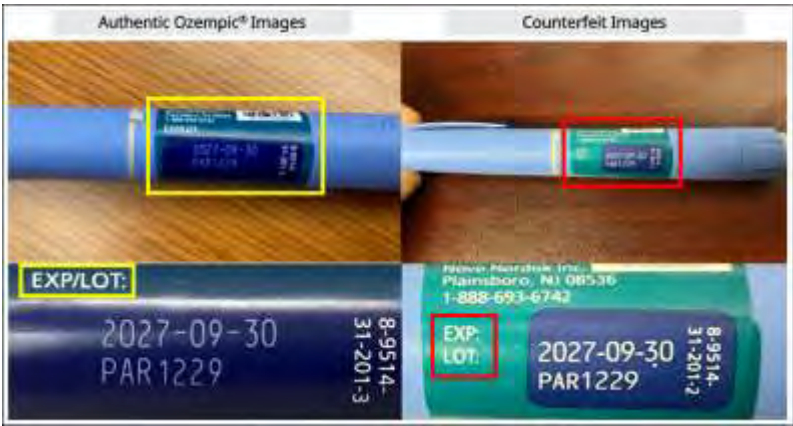
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Rapidly emerging “micro-dosing” market for GLP-1RAs without any empirical support for their efficacy



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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>

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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
- May need to be prepared for patients with SUD facing stigma for using GLP-1s



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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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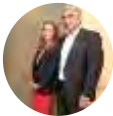


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