Winning the Rat Race: Repurposing GLP-1 Receptor Agonists for Addiction

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Intramural Research Program
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Conflicts of Interest

- No conflicts of interest to disclose
  - I will be discussing semaglutide drug brand names
  - I will be discussing off-label use of semaglutide, which is not currently FDA-approved to treat addictive disorders

Learning Objectives

1) Explain the pharmacology of GLP-1 receptor agonists

2) Evaluate the preclinical evidence in favor of repurposing GLP-1 receptor agonists as possible addiction pharmacotherapies

3) Assess some of the clinical trials studying the safety and efficacy of GLP-1 receptor agonists for addiction

4) Identify common and rare but concerning possible adverse effects of manufactured semaglutide formulations

You may have heard the hype….

“I've heard that not since the '90s with the introduction of Viagra, has there been a bigger accident in the world of medicine. And Viagra, just to remind people, was originally created to treat high blood pressure, but then people started using it to treat erectile dysfunction. And Ozempic was originally created to treat Type 2 diabetes.”

- Tonya Mosely, NPR, Fresh Air

And the Celebrities and Influencers

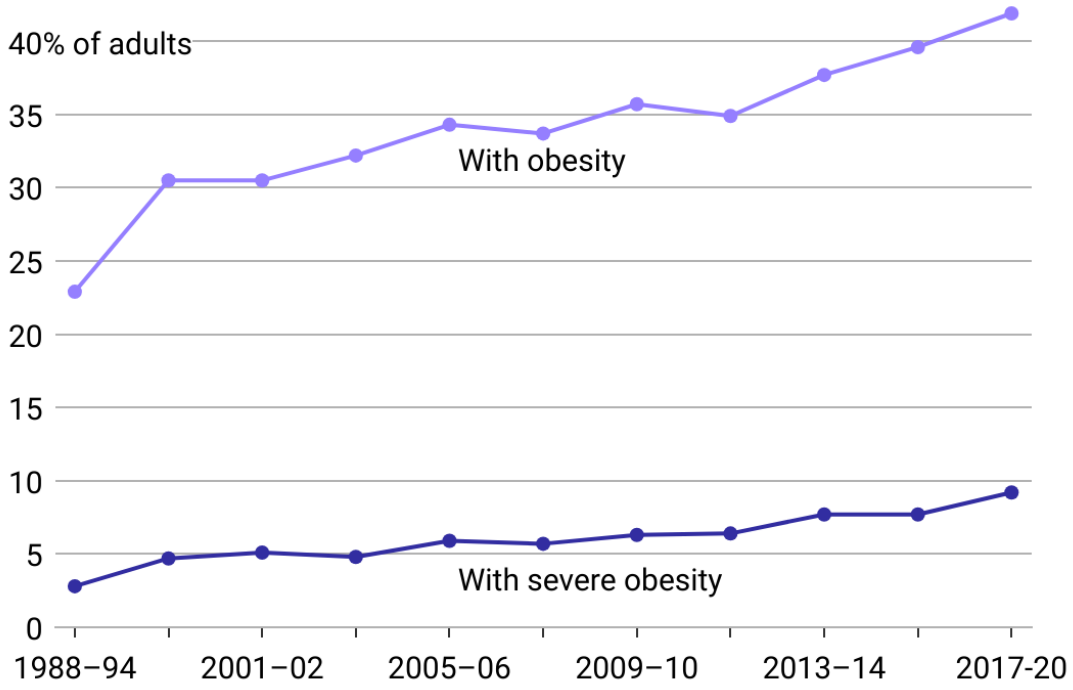
https://www.youtube.com/watch?v=Tdw2cKr5fOU

https://www.shefinds.com/collections/oprah-difference-treated-shopping-over-200-lbs-stigma/#slide-1

Why all the sudden hype?

US obesity rate on the rise since the 1980s

More than 2 in 5 adults had obesity, while nearly 1 in 10 had severe obesity, according to the latest CDC data.

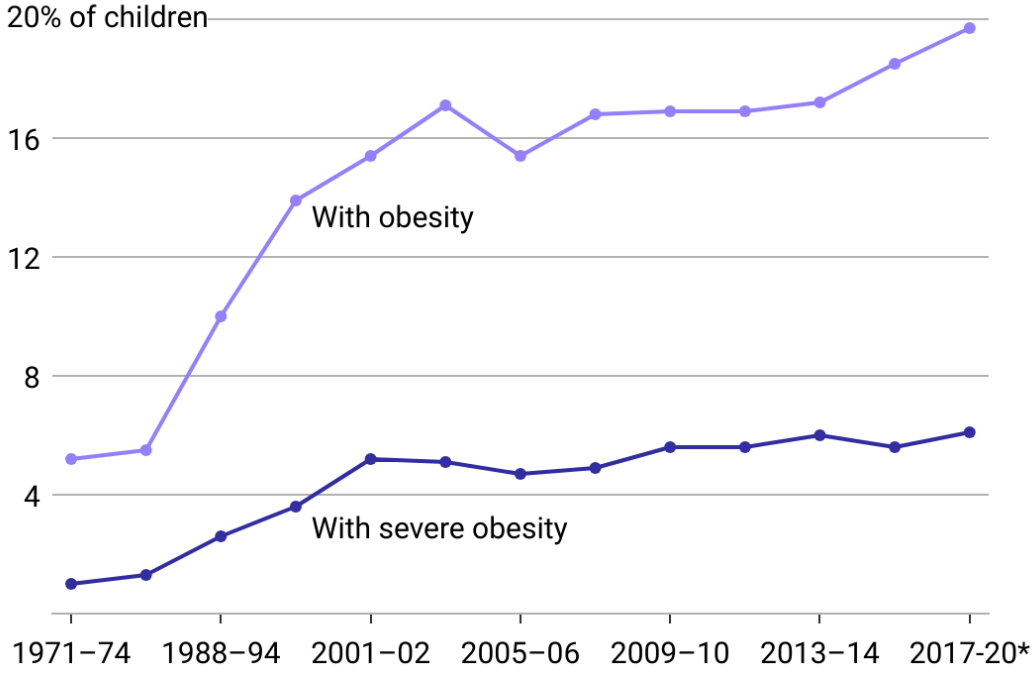


Note: Data is age-adjusted and includes adults ages 20 and over.
Because the pandemic halted data collection, the most recent data combines data for 2017 through March 2020.

Data source: Centers for Disease Control and Prevention

Childhood obesity continues to increase

Nearly 1 in 5 American children had obesity, while 6% had severe obesity, according to the latest CDC data.



Note: Data is age-adjusted and includes people from 2-19.
Because the pandemic halted data collection, the most recent data combines 2017 through March 2020 results. However, severe obesity data was unavailable, so 2017-2018 estimates are shown instead.

Data source: Centers for Disease Control and Prevention

2019

Table 1. FDA-Approved Indications for Semaglutide

Brand Name	Indication
Ozempic 2017	▶ Treatment of type 2 diabetes in adults ▶ To reduce the risk of MACE in adults with type 2 diabetes and established CVD
Rybelsus	▶ Treatment of type 2 diabetes in adults
Wegovy 6/2021	▶ Chronic weight management in patients ≥12 years old with obesity ▶ Chronic weight management in adults with overweight and at least one weight-related comorbidity (e.g., hypertension, dyslipidemia)
3/2024	▶ To reduce the risk of MACE in adults with established CVD and either obesity or overweight

CVD = cardiovascular disease; MACE = major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death)

The Medical Letter on Drugs and Therapeutics, Issue 1701, Apr. 2024

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

ABSTRACT

CONCLUSIONS:

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

fine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.

FDA-approved for this indication in 01/2025!

to 0.88; P=0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

CONCLUSIONS

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease. (Funded by Novo Nordisk; FLOW ClinicalTrials.gov number, NCT03819153.)

ford Center for Clinical Research, Department of Medicine, Stanford School of Medicine, Palo Alto, CA (K.W.M.); KfH Kidney Center, Munich, and University Hospital, Friedrich-Alexander University, Erlangen — both in Germany (J.F.E.M.); the Department of Medicine, American Heart Association Comprehensive Hyper-

tigators are listed in the Supplementary Appendix, available at NEJM.org.

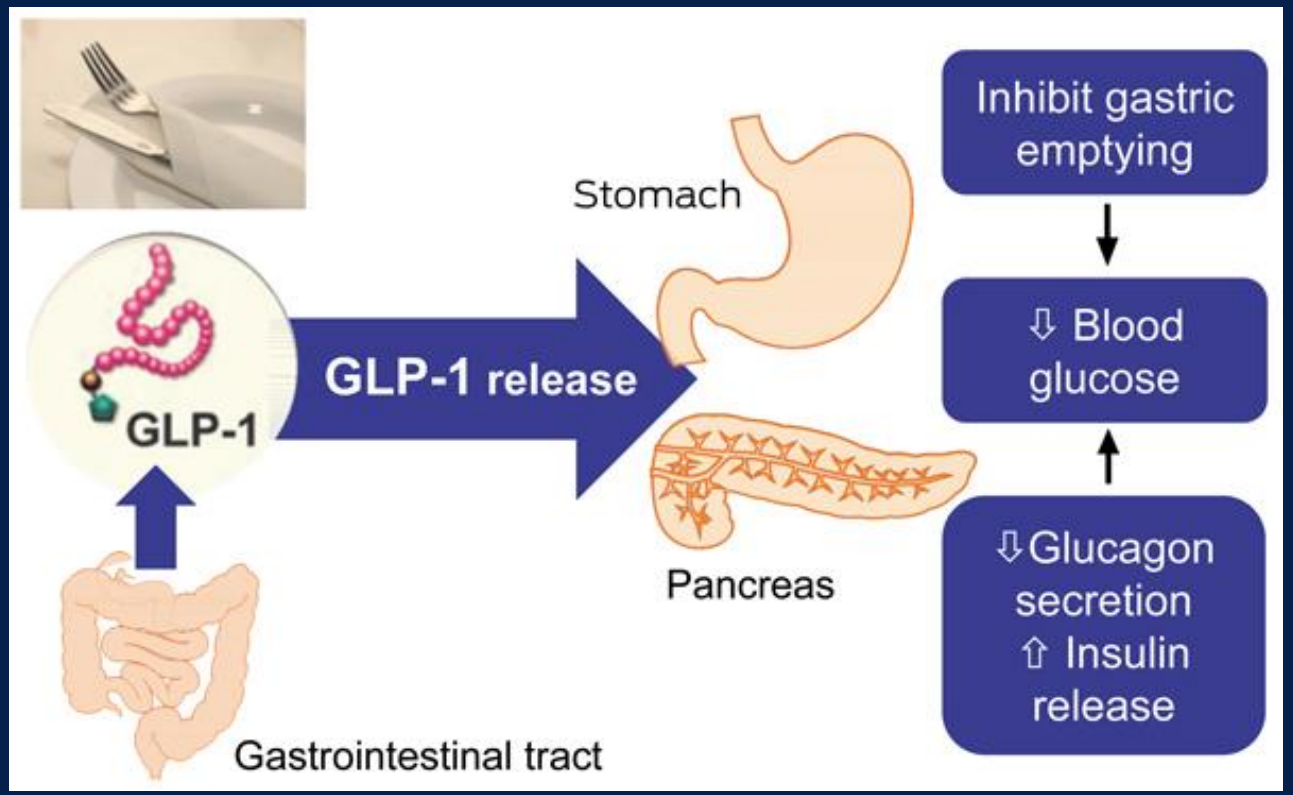
This article was published on May 24, 2024, and updated on September 17, 2024, at NEJM.org.

N Engl J Med 2024;391:109-21.
DOI: 10.1056/NEJMoa2403347

CME

Glucagon-Like Peptide-1 (GLP-1)

- Short-acting peptide with 30 amino acids
- Produced in the intestinal mucosa and pancreas
- Regulates blood glucose and food intake



Cohen ND, *et al*. (2013) *Med J Aust*

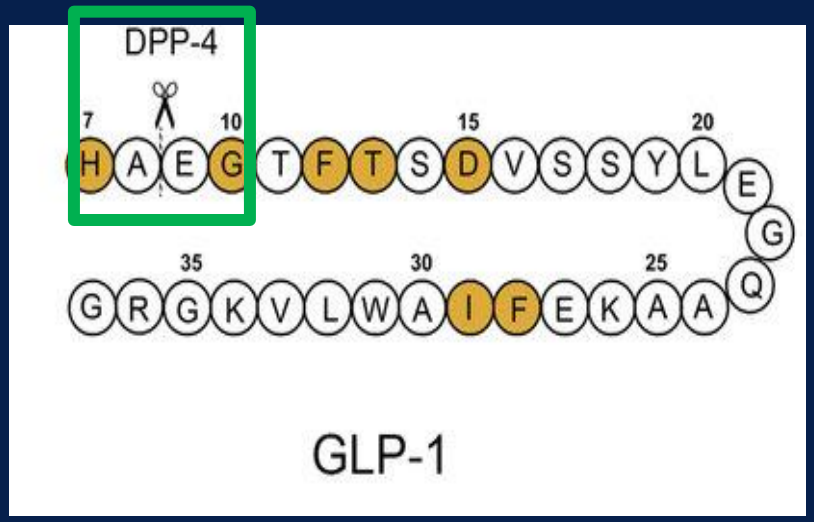
GLP-1 and GLP-1RAs

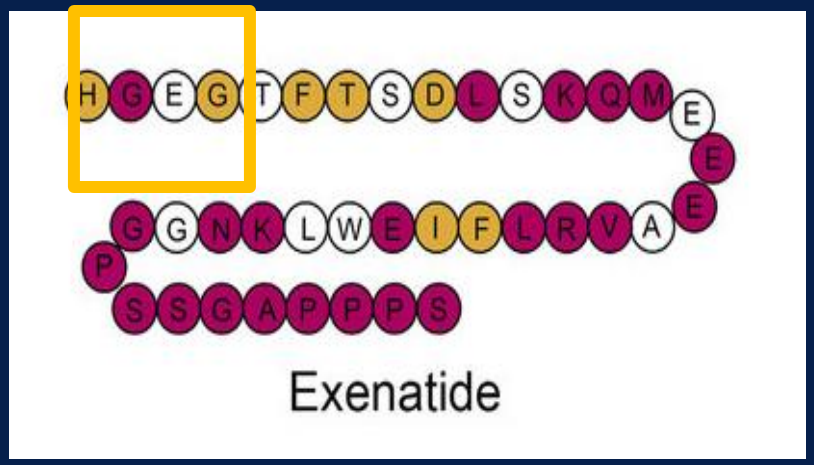
DPP-4 = Dipeptidyl Peptidase-4

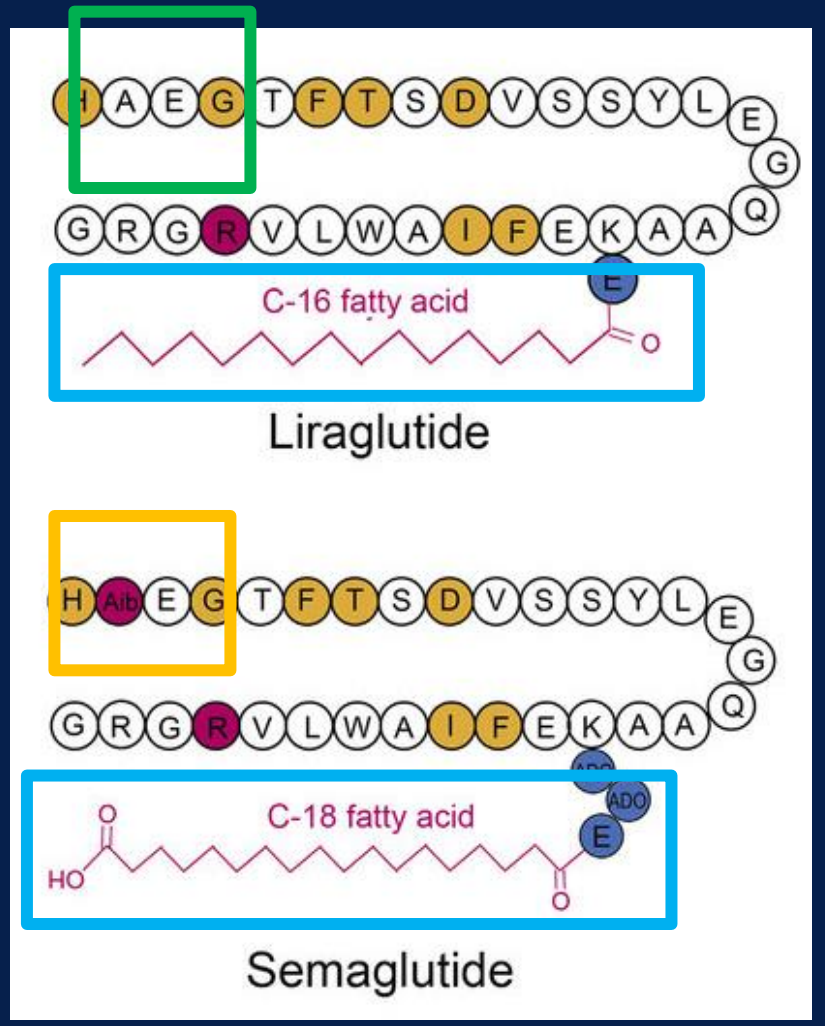
Key amino acid for potency

Substituted amino acid

Spacer

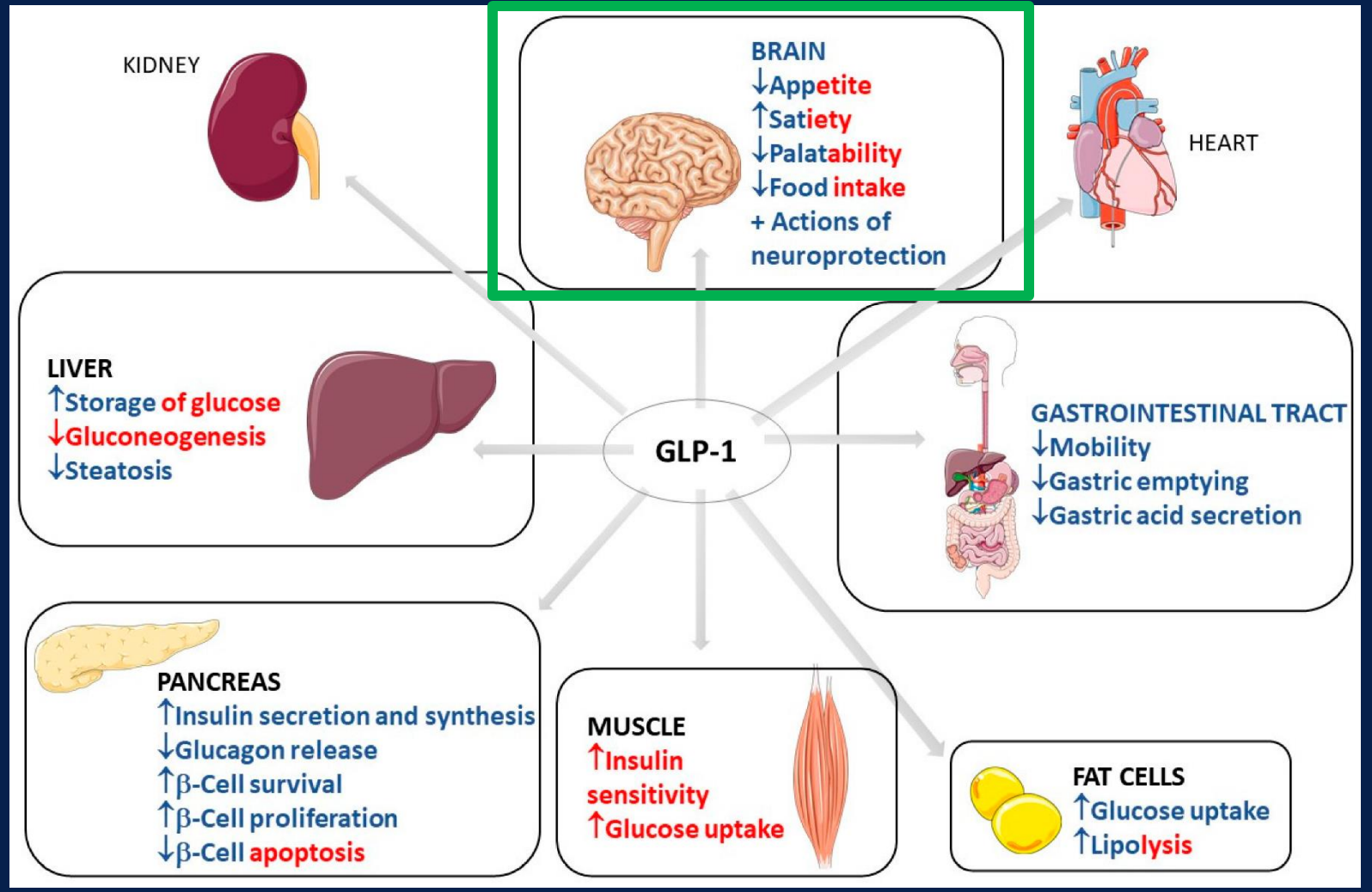






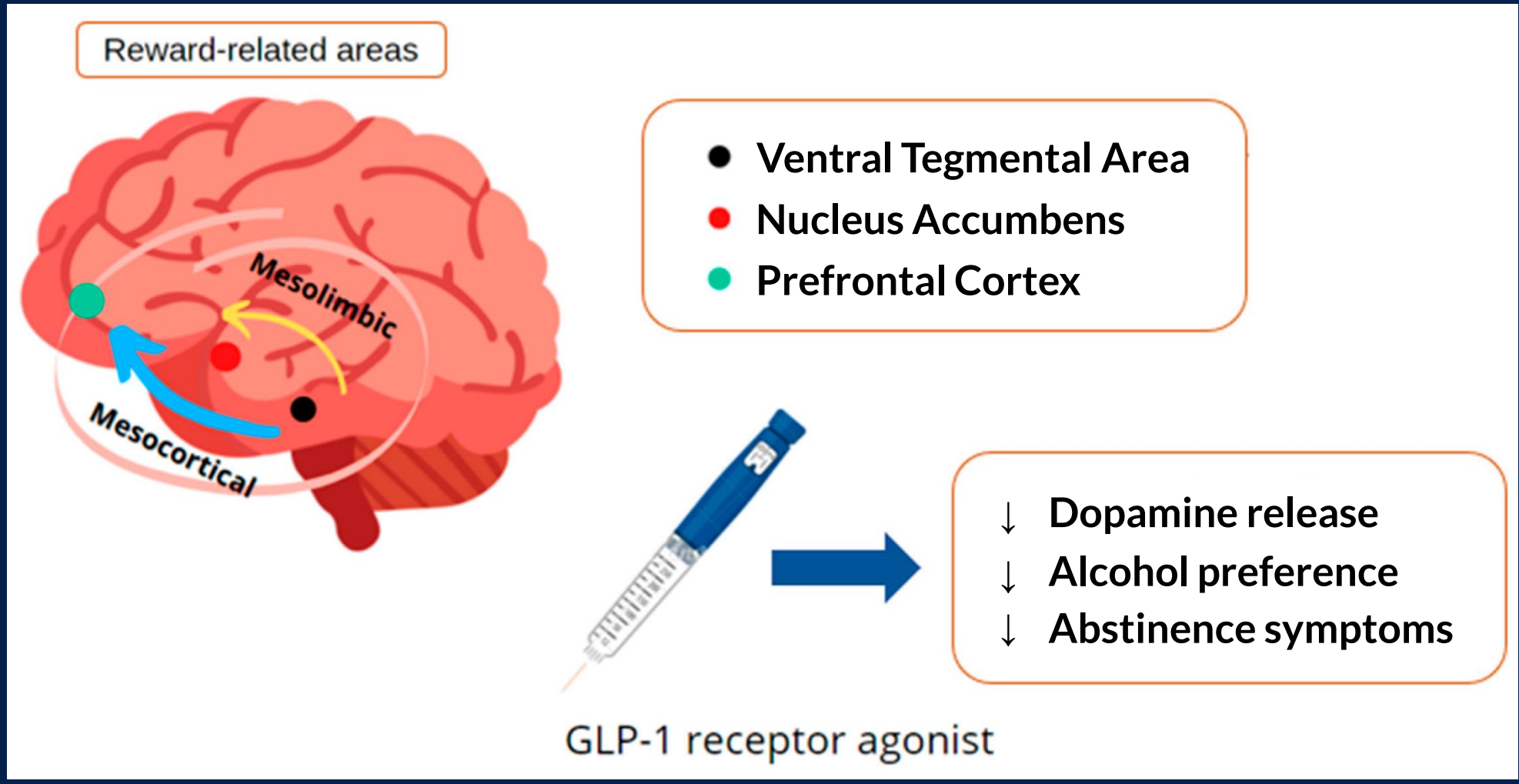
Advanced Drug Delivery Reviews. 2018;130:113-30

GLP1-RAs in Diabetes and Obesity



International Journal of Molecular Sciences, 2022, *23*(2): 739.

Possible Role of GLP-1RAs in Addiction



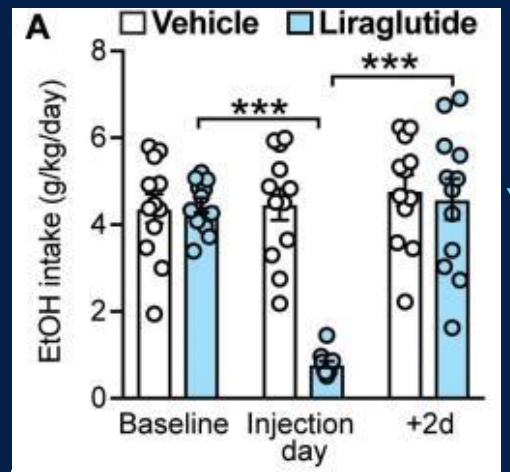
International Journal of Molecular Sciences, 2022, *23*(2): 739.

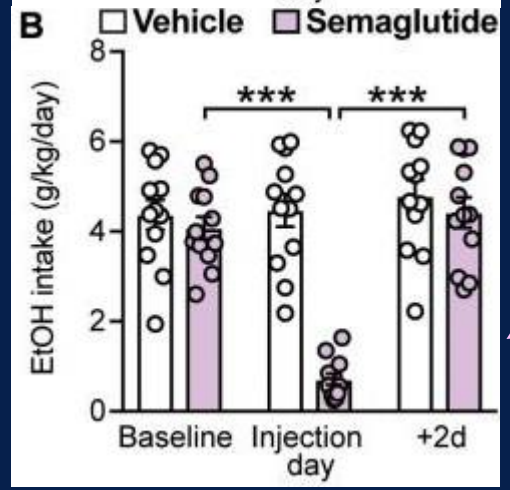
Over A Decade of Preclinical Evidence Supports a Role for GLP-1 in AUD

Study Reference	Findings
Egecioglu *et al.*, ***Psychoneuroendocrinology*** (2013) 38: 1259	Exendin 4 ↓ alcohol reward and intake in mice
Shirazi *et al.*, ***PLOS ONE*** (2013) 8: e61965	GLP-1 and Exendin 4 ↓ alcohol intake/reward in rats
*Suchankova *et al.*, ***Transl. Psychiatry*** (2015) 5: e583	AC3174 ↓ alcohol consumption in dependent mice
Vallöf *et al.*, ***Addiction Biology*** (2016) 21: 422	Liraglutide ↓ alcohol reward and intake in rats
Sørensen *et al.* ***Alcohol Clin Exp Res*** (2016) 40: 2247	Exendin 4 ↓ self-administration of IV alcohol in mice
*Marty *et al.* ***Frontiers in Neuroscience*** (2020) 14: 599646	Liraglutide and semaglutide ↓ alcohol intake in rats
Aranas *et al.* ***EBioMedicine*** (2023) 93: 104642	Semaglutide ↓ alcohol intake and relapse in rats
*Chuong *et al.* ***JCI Insight*** (2023) 8: e170671	Semaglutide ↓ binge drinking of alcohol in mice/rats

Administration of GLP-1 or GLP-1R agonists to rodents decreases drinking and attenuates the reinforcing properties of alcohol, suggesting that the GLP-1R is a potential target for treating AUD.

Intermittent Access 2-Bottle Choice Rat Study with Liraglutide and Semaglutide

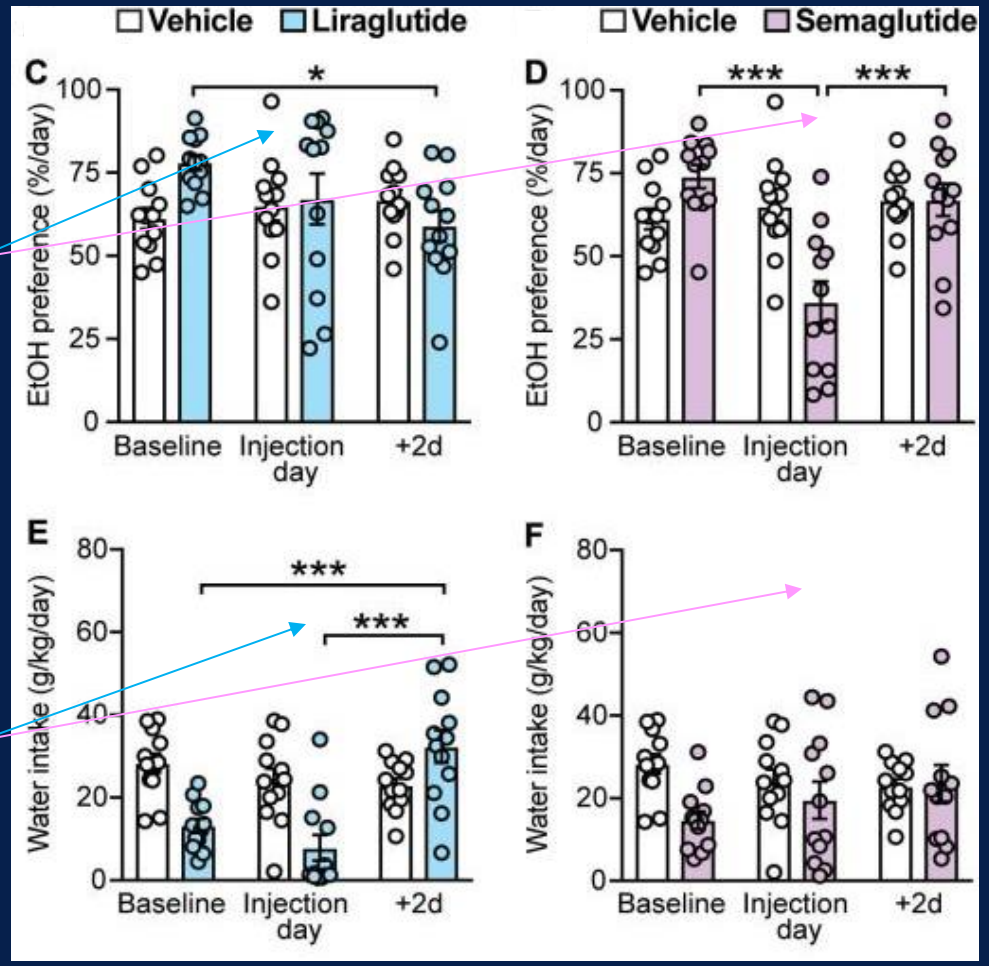




Both liraglutide and semaglutide decreased EtOH intake

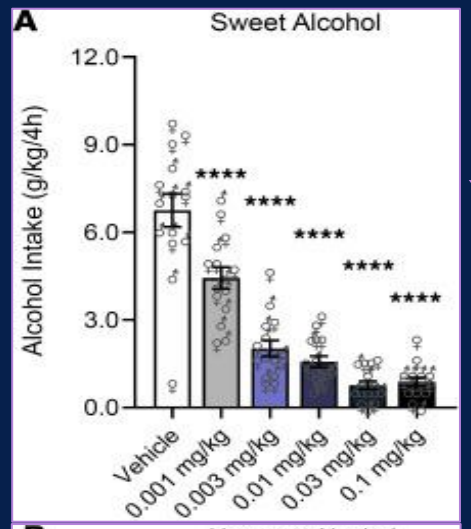
Both liraglutide and semaglutide decreased EtOH preference, but semaglutide decreased it more

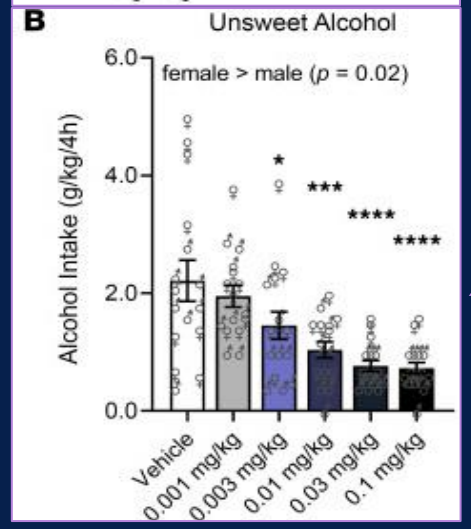
Liraglutide also nonspecifically decreased water intake, while semaglutide did not



Marty, V. N., *et al.* (2020) *Frontiers in Neuroscience*, *14*: 599646.

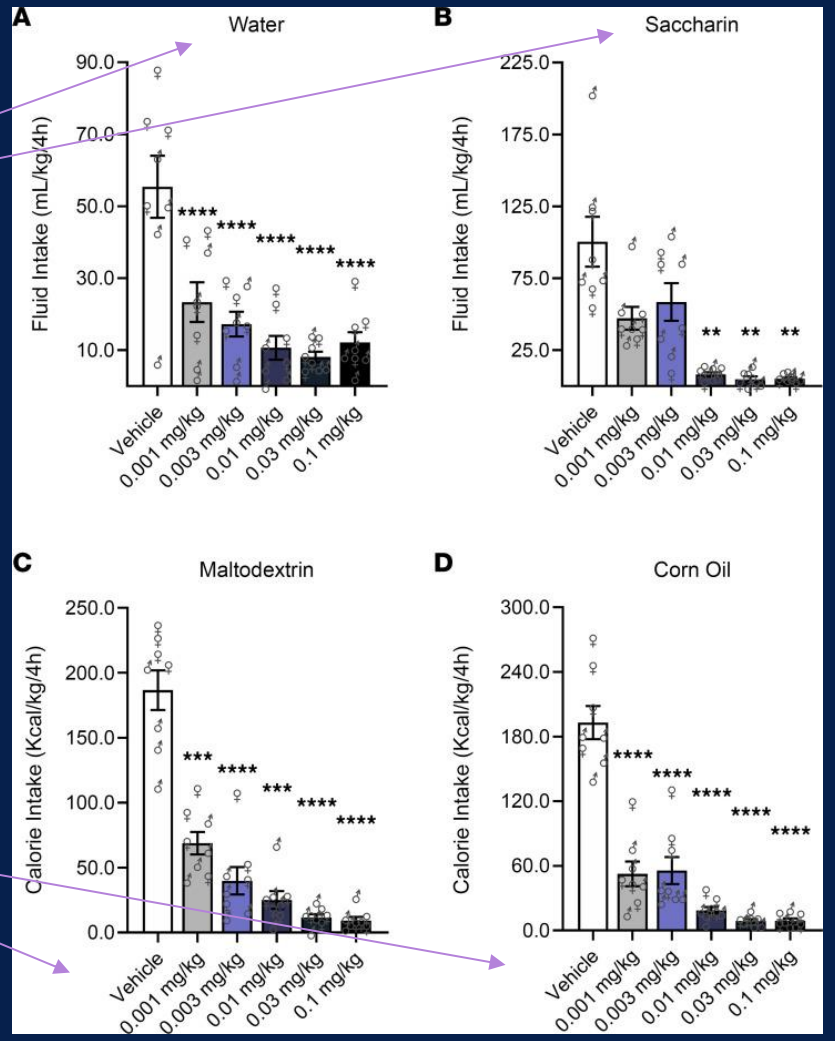
Semaglutide Dose-Dependently Reduces Binge-Like Drinking in Drinking-in-the-Dark Mice





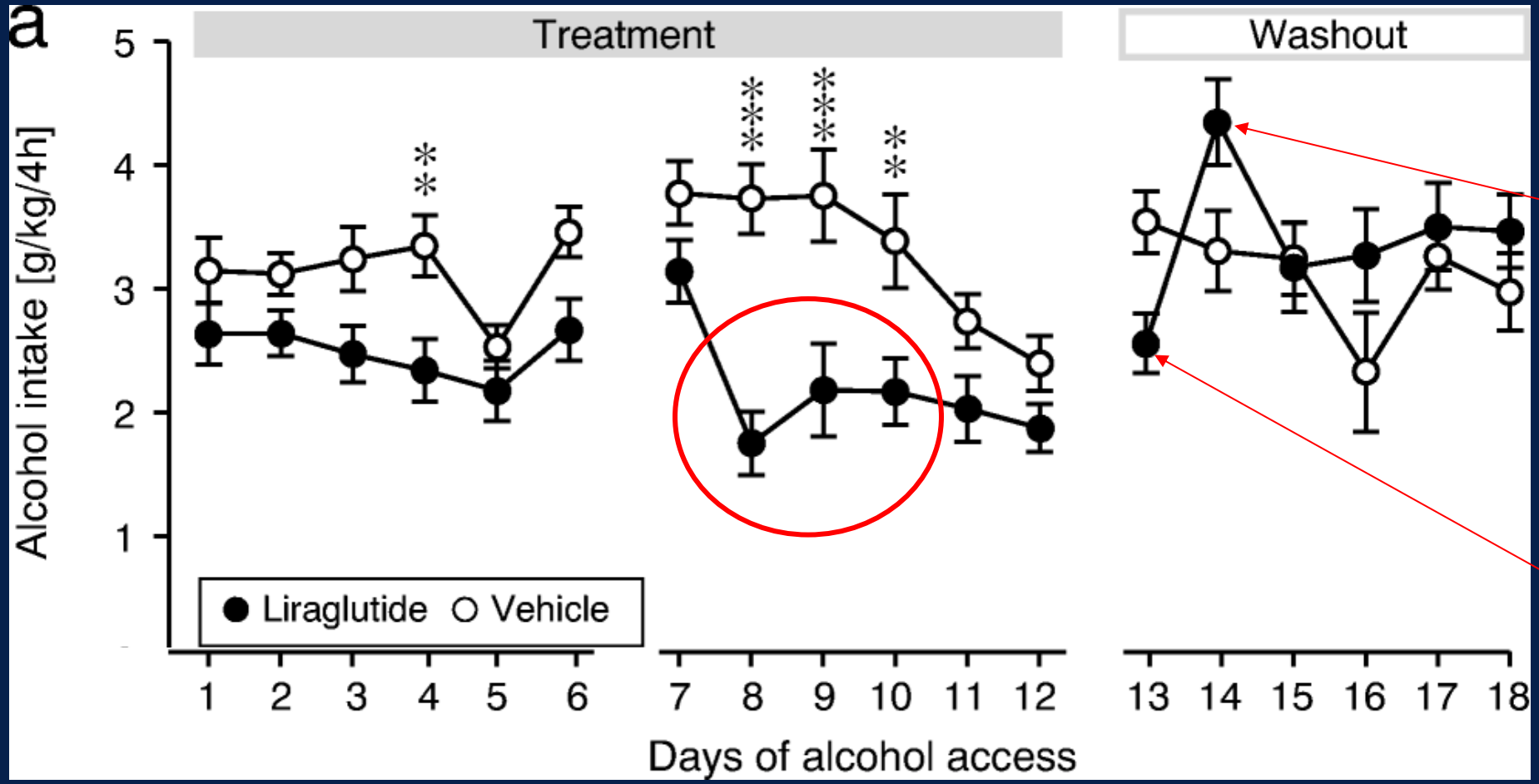
Both sweet and unsweet alcohol drinking were dose-dependently decreased

Semaglutide also decreased fluid intake, including water, a noncaloric sweet solution (saccharin), and two unsweet caloric solutions (maltodextrin and corn oil)



Chuong, V. *et al.,* (2023). *JCI insight*, *8*(12): e170671.

Liraglutide Administration Decreased Alcohol Drinking in Dependent Vervet Monkeys

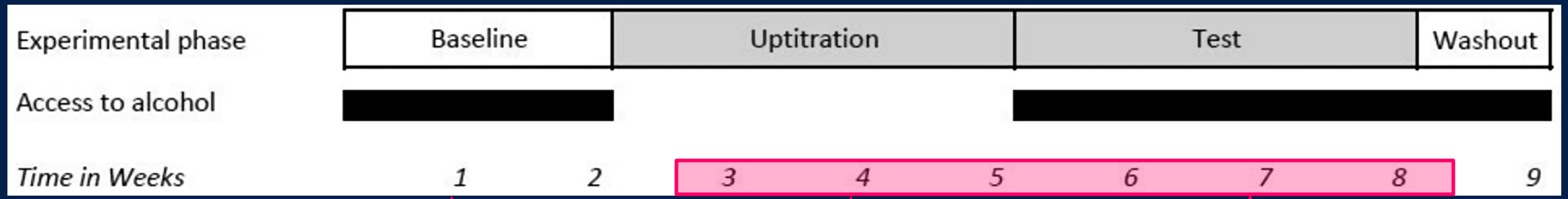


Apparent rebound effect in drinking occurred on the second day of washout

Alcohol intake remained decreased x1 day after stopping liraglutide

Thomsen, M., *et al.* (2019) *Psychopharmacology*, *236*: 603-611.

Semaglutide Administration Decreased Alcohol Drinking in Alcohol-Preferring Vervet Monkeys



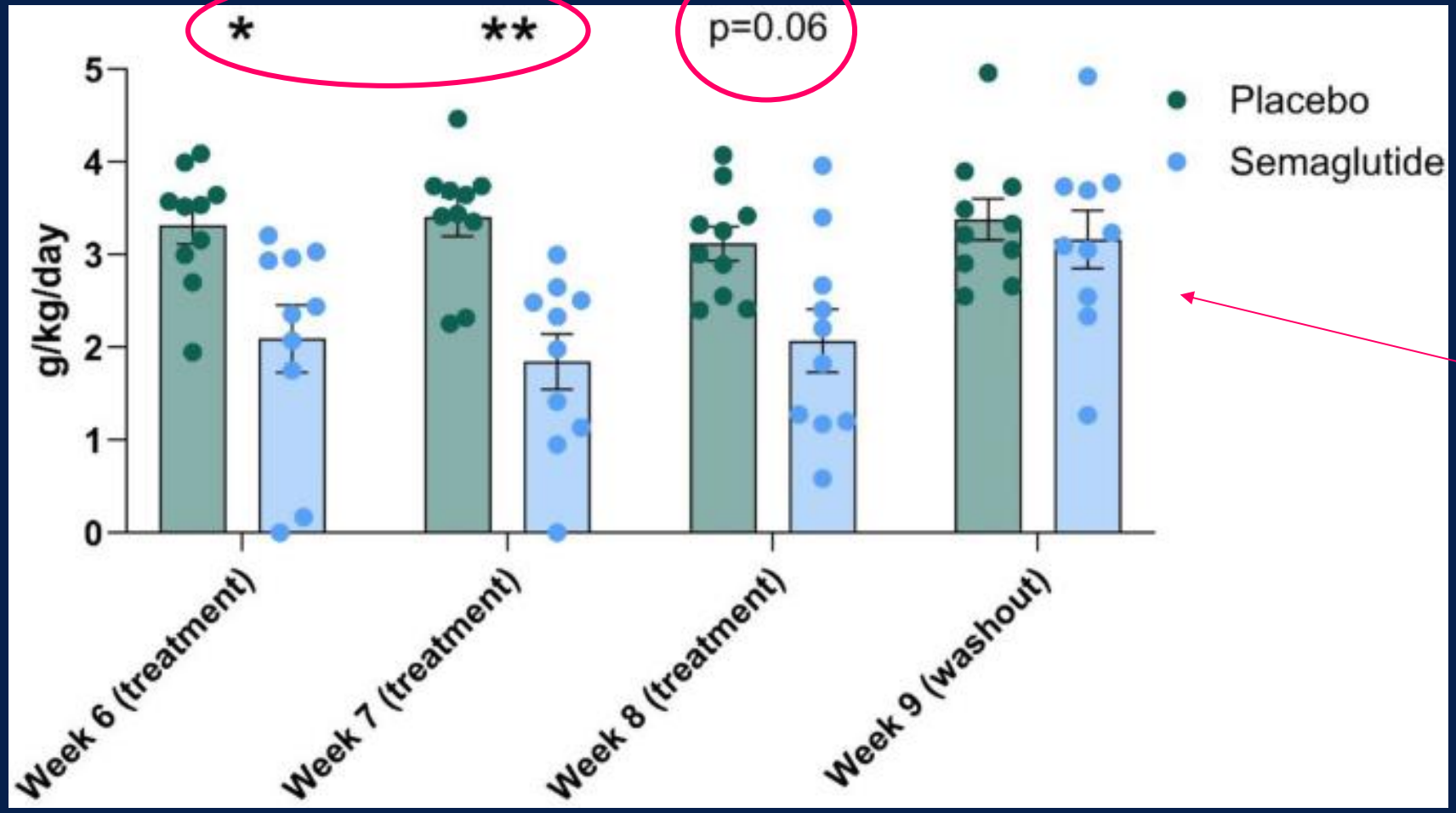
Two weeks of alcohol self-administration to identify "alcohol-preferring" individuals

Three weeks dose up-titration (0.01 mg/kg => 0.03 mg/kg => 0.05 mg/kg dosed 2x/week)

Three weeks of semaglutide maximum tolerated dosing + EtOH

Fink-Jensen, A., *et al.* (2025) *Psychopharmacology*, *242*: 63-70.

Semaglutide Administration Decreased Alcohol Drinking in Alcohol-Preferring Vervet Monkeys



No significant difference in drinking in the week after the drug was stopped.

Fink-Jensen, A., *et al.* (2025) *Psychopharmacology*, *242*: 63-70.

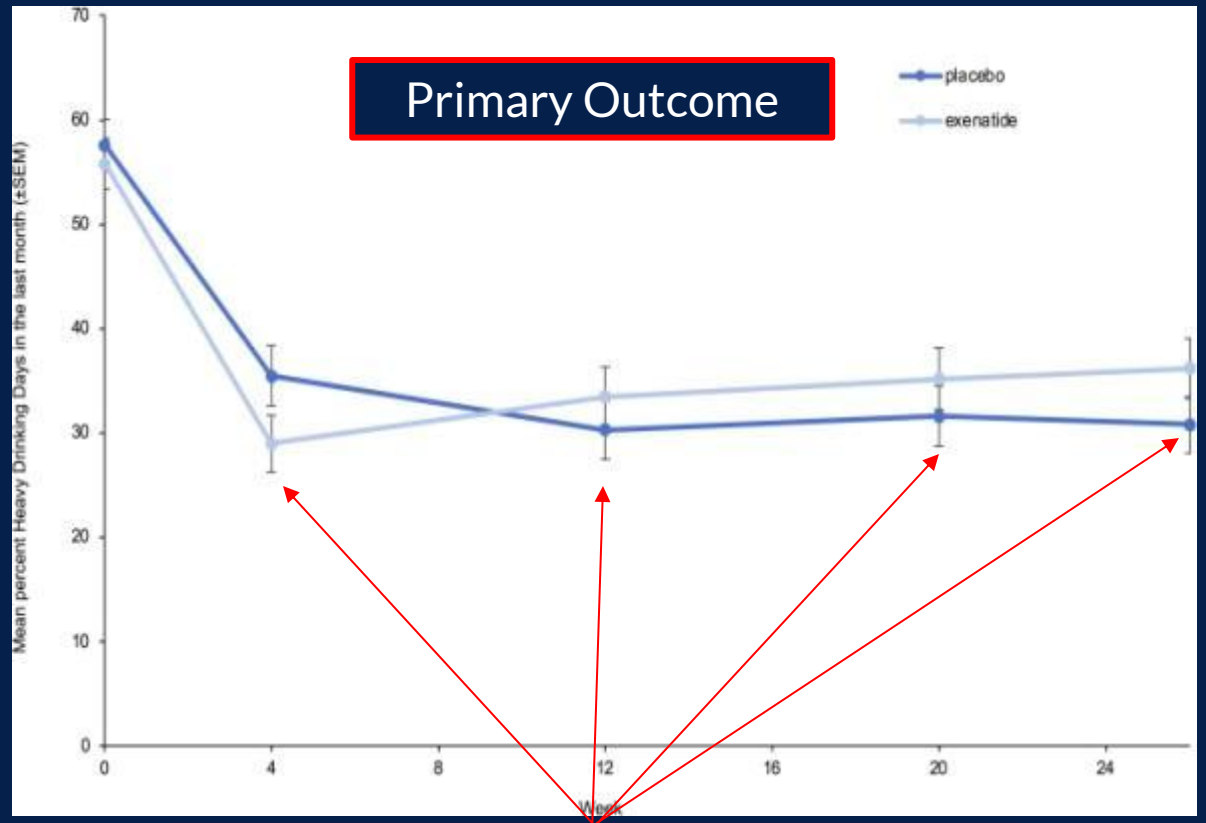
Anecdotal/Correlational Human Evidence of GLP-1RA Efficacy for AUD

Study Reference	Findings
*Suchankova, ***Transl. Psychiatry*** (2015) 5: e583	Variation in *GLP1R* ass'd w/ AUD (genetic association study)
Wium-Anderson, ***Basic & Clin. Pharm. & Tox.*** (2022) 131: 372-379	GLP-1RA tx ass'd w/ lower risk of alcohol-related events (national registry cohort/case series)
*Farokhnia, ***Addict. Biol.*** (2022) 27: e13211	↑ GLP-1RA expression in AUD pts (post-mortem brain study) Alcohol administration ↓ blood [GLP-1] (experimental lab studies)
*Farokhnia, ***Scientific Reports*** (2022) 12: 13027	GLP-1R gene variants ass'd w/ brain connectivity (imaging/genetic study)
Quoddos, ***Scientific Reports*** (2023) 13: 20998	Semaglutide/tirzepatide improved AUD (social media post analysis)
Richards, ***J. of Clin. Psych.*** (2023) *85*(1): 50515	Semaglutide improved AUD (six-person case series)
Bremmer, ***J. Stud. on Alc. & Drugs*** (2024) 85: 5-10	GLP-1RAs improve AUD (Reddit post pharmacovigilance)
Wang, ***Nature Communications*** (2024) 15: 4548	Semaglutide ↓ AUD incidence/recurrence (retrospective EMR study)

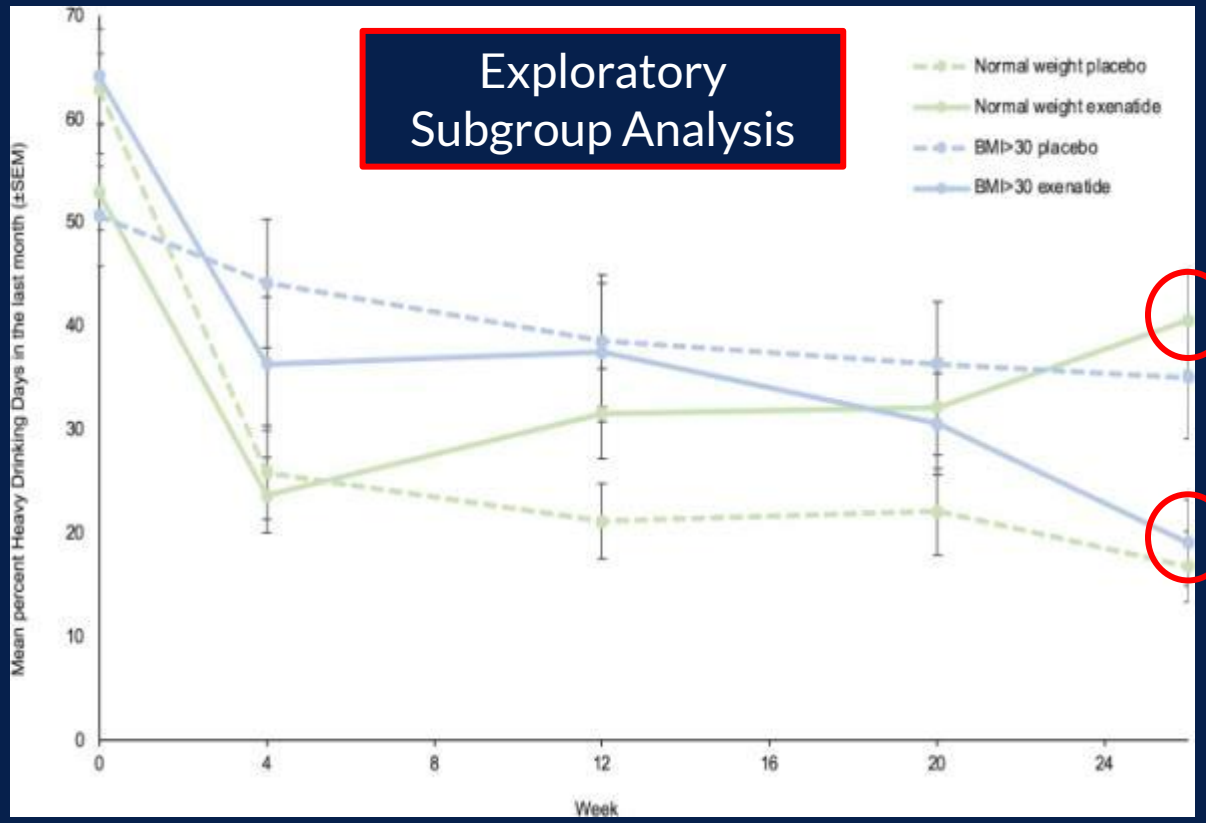
These observational and large-data studies in humans are suggestive of GLP-1RA efficacy for treating AUD, and they provide additional support for testing these compounds as treatments for AUD, but they cannot substitute for rigorous human randomized controlled trials.

https://www.chargrilled.us/t-shirts/Alcohol-Loading-Please-Wait-t-shirt.m

First Published Trial of GLP-1RA in AUD



After an initial decrease in heavy drinking days in both groups, there was no further significant difference



In patients with BMI>30 kg/m2, exenatide reduced heavy drinking days by 23.6% (CI -44.4—2.7, p=0.034)

Klausen, M. K., *et al.* (2022) *JCI insight*, 7(19): e159863

Summary of Semaglutide AUD Trials

Study Location	SAUD (UNC-NC)	SEMALCO (Denmark)	Rybelsus (CU-CO)	STAR-T (OSU-OK)	STAR-B (NIDA-MD)
Enrollment	48	108	135	80	52
Drug Form	Injectable	Wegovy	Rybelsus	Injectable	Injectable
Max Dose	1.0 mg	2.4 mg	7 mg	1 mg	2.4 mg
Dosing	9 weeks	26 weeks	8 weeks	12 weeks	20 weeks
Primary Outcome	BrAC, alcohol consumed	TLFB (% heavy drinking days)	Craving (VAS score)	Standard drinks/week	AEs, standard drinks/week
Completion	4/2024	8/2025	*6/2025	*12/2025	*12/2030
Current Status	Completed, published 2/25	Done enrolling (analysis)	Completing enrolling	Completing enrolling	Currently enrolling

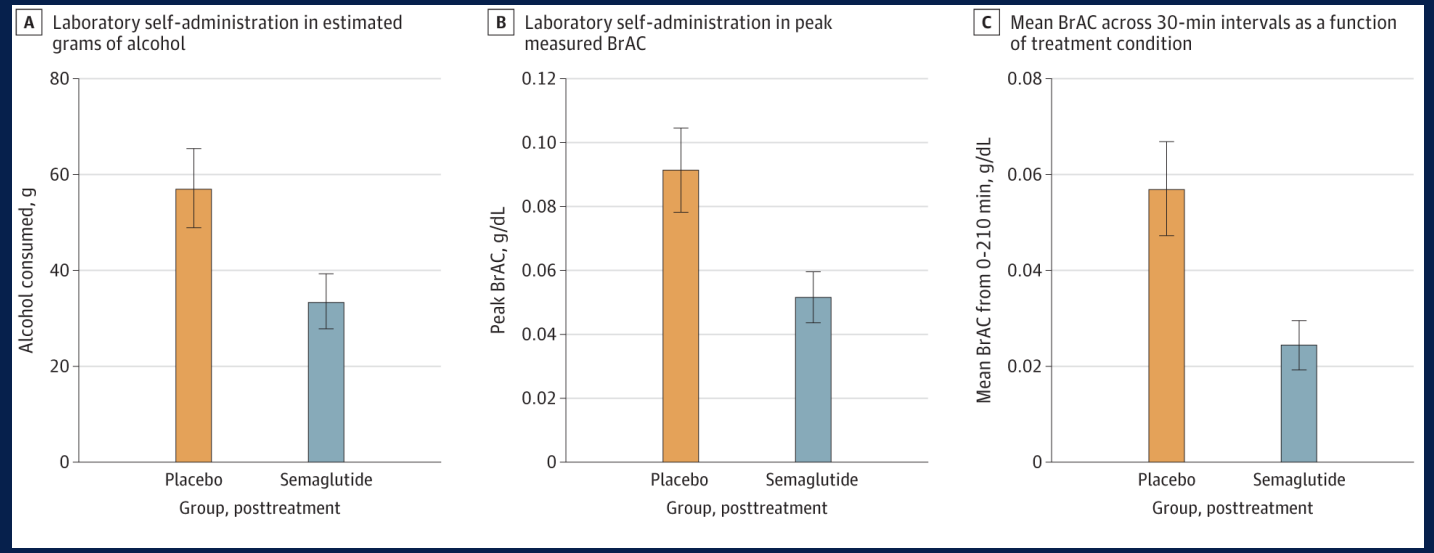
Clinicaltrials.gov; Hendershot, C. *et al.* (2025) *JAMA Psychiatry*

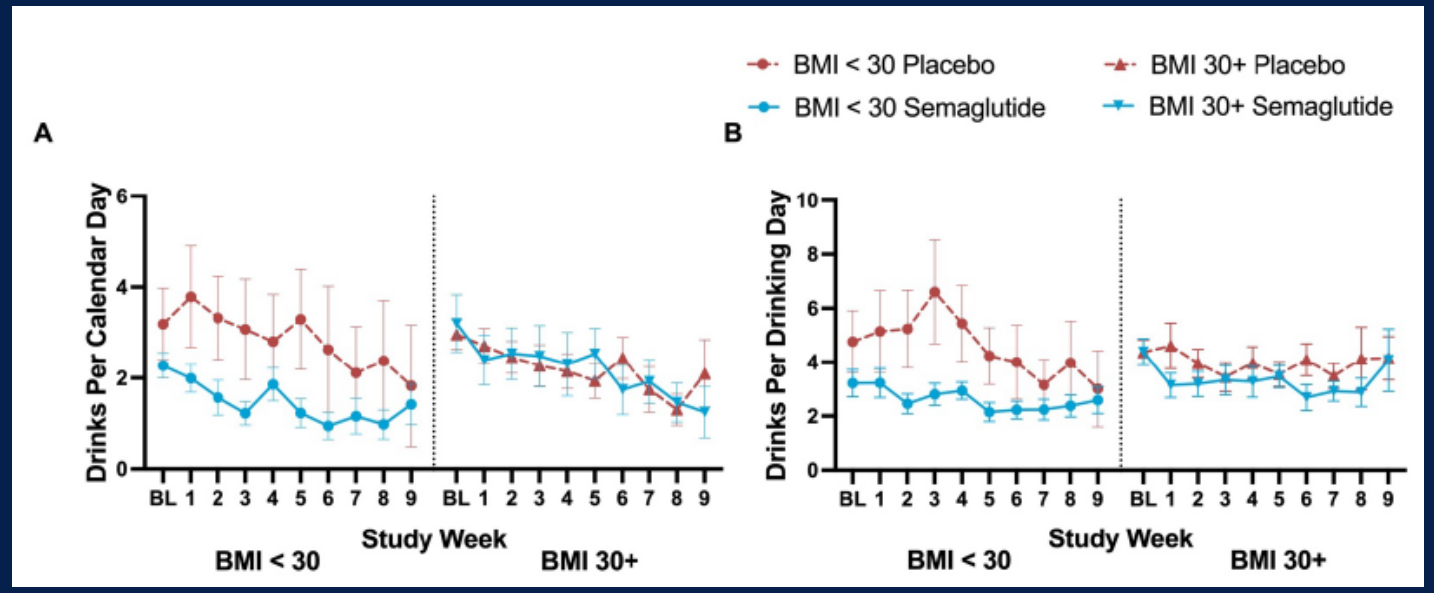
First Published Trial of Semaglutide in AUD

48 AUD patients, 9 weeks, tested low-dose semaglutide vs. placebo

Primary outcome: laboratory alcohol self-administration

Exploratory BMI endpoint suggests that the drug is more effective for *__lower__* BMIs





Original Investigation

February 12, 2025

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder

A Randomized Clinical Trial

Christian S. Hendershot, PhD[1,2,3]; Michael P. Bremmer, MA[3,4]; Michael B. Paladino, BS[3,4]; et al

Author Affiliations | Article Information

JAMA Psychiatry. Published online February 12, 2025. doi:10.1001/jamapsychiatry.2024.4789

Reported Adverse Events (AEs) in UNC Trial of GLP-1RAs in AUD Patients

	Semaglutide			Placebo		
	0.25 mg	0.50 mg	Total	"0.25 mg"	"0.50 mg"	Total
Total N (%)	24 (100%)	23 (95.8%)	24 (100%)	24 (100%)	21 (87.5%)	24 (100%)
Any AE	19 (79.2%)	19 (82.6%)	22 (91.7%)	16 (66.7%)	12 (57.1%)	18 (75.0%)
Serious AE	0	0	0	0	0	0
Mild AE	19 (79.2%)	19 (82.6%)	22 (91.7%)	16 (66.7%)	11 (52.4%)	18 (75.0%)
Moderate AE	4 (33.3%)	5 (21.7%)	8 (33.3%)	2 (8.3%)	2 (9.5%)	4 (16.7%)
Severe AE	0	2 (8.7%)	2 (8.3%)	0	1 (4.8%)	1 (4.2%)
↓ Appetite	15 (62.5%)	16 (69.6%)	18 (75.0%)	9 (37.5%)	5 (23.8%)	10 (41.7%)
Nausea	11 (45.8%)	11 (47.8%)	17 (70.8%)	3 (12.5%)	2 (9.5%)	4 (16.7%)
Constipation	8 (33.3%)	9 (39.1%)	12 (50.0%)	1 (4.2%)	1 (4.8%)	2 (8.3%)
Diarrhea	4 (16.7%)	7 (30.4%)	10 (41.7%)	7 (29.2%)	5 (23.8%)	9 (37.5%)

Hendershot, C. *et al.* (2025) *JAMA Psychiatry*

Semaglutide Therapy for Alcohol Reduction (STAR)

Two Harmonized RCTs

Oklahoma State University

NCT05891587
PI: W. Kyle Simmons

NIDA IRP/TAMB

NCT06015893
PI: Lorenzo Leggio

Clinicaltrials.gov

RECRUITING

Semaglutide Therapy for Alcohol Reduction (STAR)

ClinicalTrials.gov ID NCT06015893

Sponsor National Institute on Drug Abuse (NIDA)

Information provided by National Institutes of Health Clinical Center (CC) (National Institute on Drug Abuse (NIDA)) (Responsible Party)

Last Update Posted 2024-02-15

+ Expand all content — Collapse all content

Study Details | Researcher View | No Results Posted | Record History

On this page

- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Publications

Study Overview

Brief Summary

Background:

Alcohol use disorder (AUD) is a problematic pattern of alcohol use accompanied by clinically significant medical consequences. Medications can help most people reduce their drinking, but the number is limited, and additional treatment options are needed.

Objective:

Study Start (Estimated)

2024-02-20

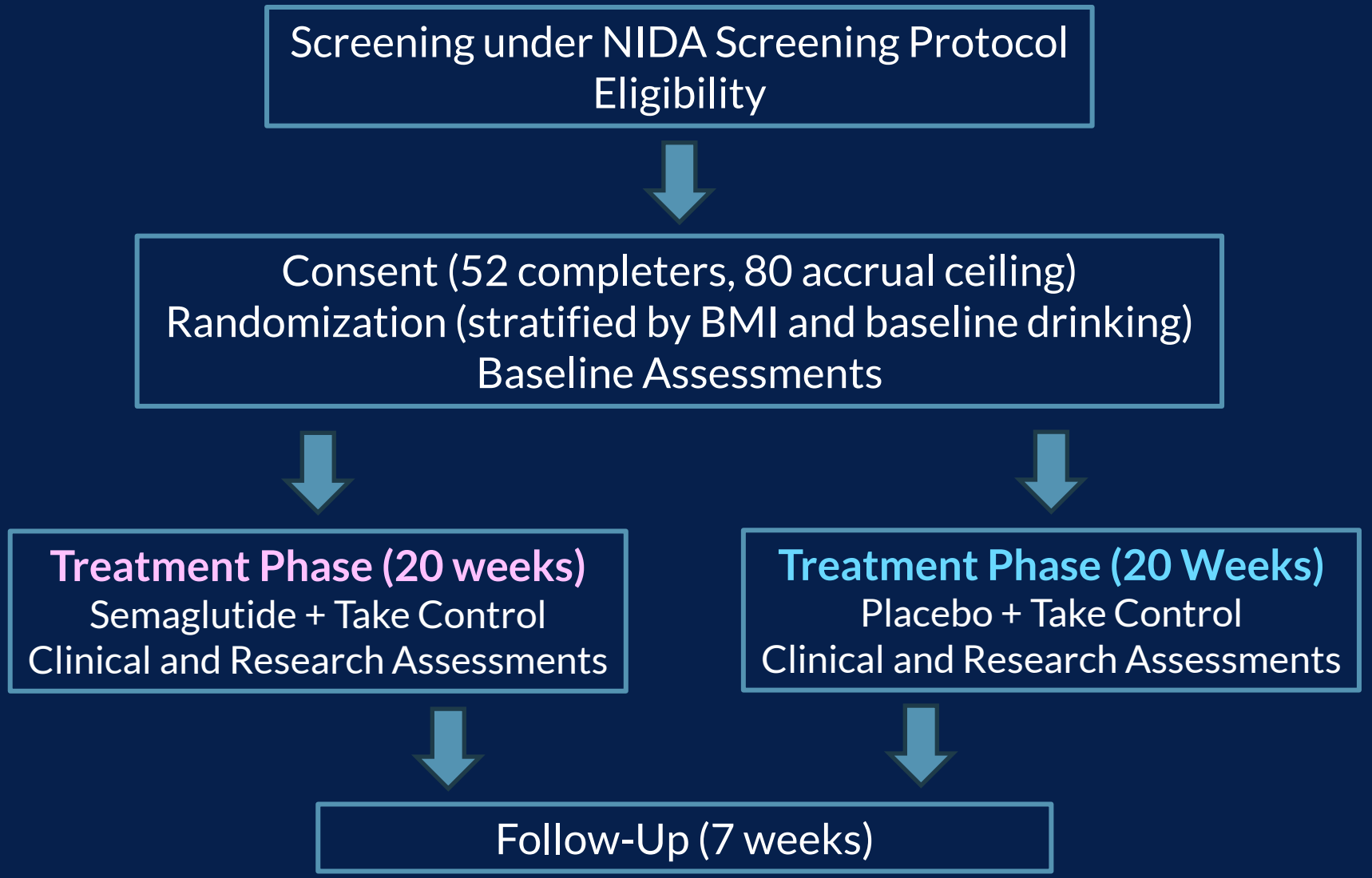
Primary Completion (Estimated)

2030-12-31

Study Completion (Estimated)

Schema for STAR-B

- **Study Design:**
  - **Randomized**
  - **Double-blinded**
  - **Placebo-controlled**
  - **Outpatient**
  - **20 weeks!**



Inclusion/Exclusion Criteria

Inclusion

- Alcohol Use Disorder (DSM-5)
- Age 18+
- Heavy Drinking (28-Day TLFB)
  - >7 (♀) or >14 (♂) drinks/week
  - 4+ days of the last 28 days with >3 (♀) or >4 (♂) drinks
- CIWA<10

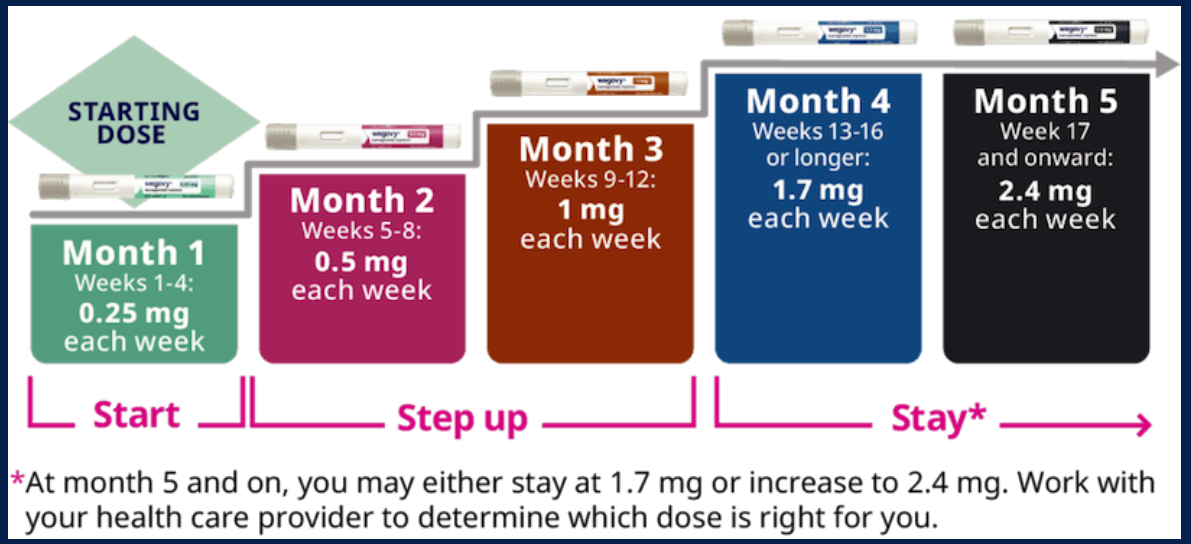
Exclusion

- Metabolic
  - BMI outside 23-50 kg/m^2
  - Malnourished (NRS-2002)
  - Diabetic (HbA1c ≥6.5)
  - Weight loss/diabetes/AUD medications or bariatric surgery
- Unstable Medical Conditions
- MRI or VR Contraindications

Study Interventions

Visit / Week # →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Follow up
Study Drug or Placebo (mg)	0.25	0.25	0.25	0.25	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.0	1.7	1.7	1.7	1.7	2.4	2.4	2.4	2.4	
Take Control	X			X			X			X			X			X			X		

https://www.rethinkingdrinking.niaaa.nih.gov/



https://www.wegovy.com/taking-wegovy/dosing-schedule.html

Semaglutide Dosing Pens

Ozempic

FDA-approved for diabetes

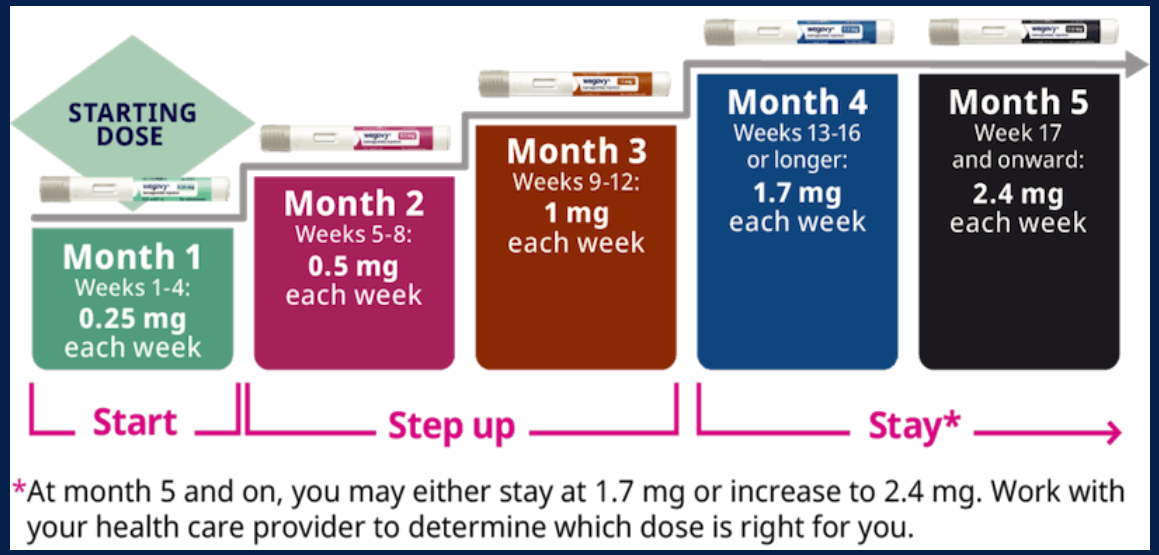
Wegovy

FDA-approved for obesity

https://www.ozempic.com/

https://www.wegovy.com/

Semaglutide Therapy for Alcohol Reduction (STAR)



https://www.wegovy.com/taking-wegovy/dosing-schedule.html, https://www.ozempic.com/how-to-take/ozempic-dosing.html

Outcomes

Primary

- Safety and Tolerability
  - Number/severity of Adverse Events (AEs)
  - Number of people who reach target dose (2.4 mg)
- Early Efficacy
  - Change in self-reported drinks/week from baseline to end of study
    - 28-Day Timeline Followback (TLFB)

Secondary

- Other Drinking Outcomes
  - Heavy drinking days
  - WHO drinking risk levels
  - Phosphatidylethanol (PEth) levels
- Changes in Study Tasks
  - Virtual Reality (Food Craving)
  - Cue Reactivity (Alcohol Craving)
  - Brain fMRI (resting, task-based)

28 Day TLFB (Binge Drinking Pattern)

01/03/2024		0.000
01/02/2024		0.000
01/01/2024	NYD	0.000
12/31/2023	NYE	6.000
12/30/2023		5.000
12/29/2023		2.000
12/28/2023		0.000
12/27/2023		0.000
12/26/2023		0.000
12/25/2023	Christmas	0.000
12/24/2023		5.000
12/23/2023		4.000
12/22/2023		5.000
12/21/2023		0.000
12/20/2023		0.000
12/19/2023		0.000
12/18/2023		0.000
12/17/2023		0.000
12/16/2023		5.000
12/15/2023		3.000
12/14/2023		2.000
12/13/2023		3.000
12/12/2023		0.000
12/11/2023		0.000
12/10/2023		0.000
12/09/2023		3.000
12/08/2023	Hanukkah	0.000

Score(s)

Type	Score
Average number of drinks per day (last 28 days)	1.714
Days with >= 5 drinks	6
Days with >= 4 drinks	7

28 Day TLFB (Daily Drinking Pattern)

02/19/2024	Presidents' Day	14.000
02/18/2024		10.000
02/17/2024		14.000
02/16/2024		14.000
02/15/2024		12.000
02/14/2024	Valentine's Day	12.000
02/13/2024		12.000
02/12/2024		12.000
02/11/2024		12.000
02/10/2024		14.000
02/09/2024		12.000
02/08/2024		12.000
02/07/2024		12.000
02/06/2024		12.000
02/05/2024		12.000
02/04/2024		14.000
02/03/2024		16.000
02/02/2024		12.000
02/01/2024		12.000
01/31/2024		12.000
01/30/2024		12.000
01/29/2024		12.000
01/28/2024		14.000
01/27/2024		14.000
01/26/2024		12.000
01/25/2024		12.000
01/24/2024		12.000
01/23/2024		12.000

Score(s)

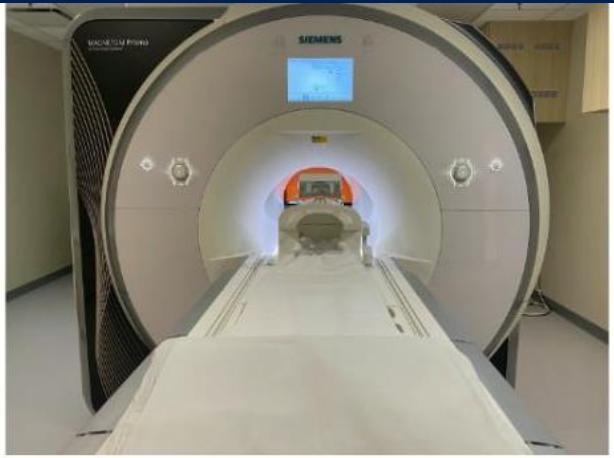
Type	Score
Average number of drinks per day (last 28 days)	12.571
Days with >= 5 drinks	28
Days with >= 4 drinks	28

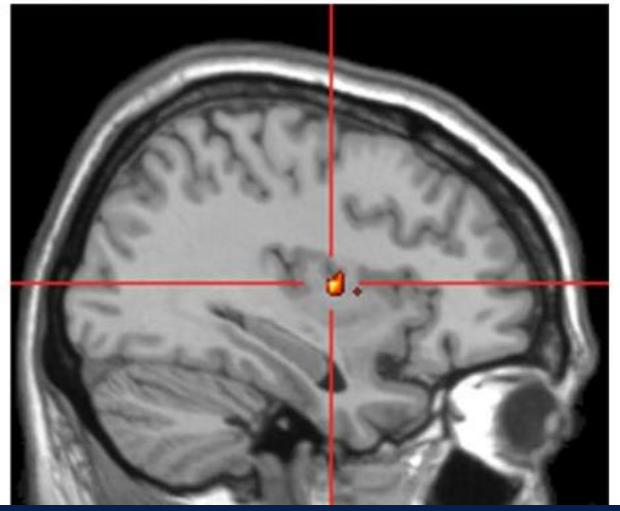
Virtual Reality Buffet

Virtual Reality food buffet task : Participants presented with a virtual reality food buffet cafeteria, with caloric and macronutrient food selection behaviors recorded for subsequent analyses.

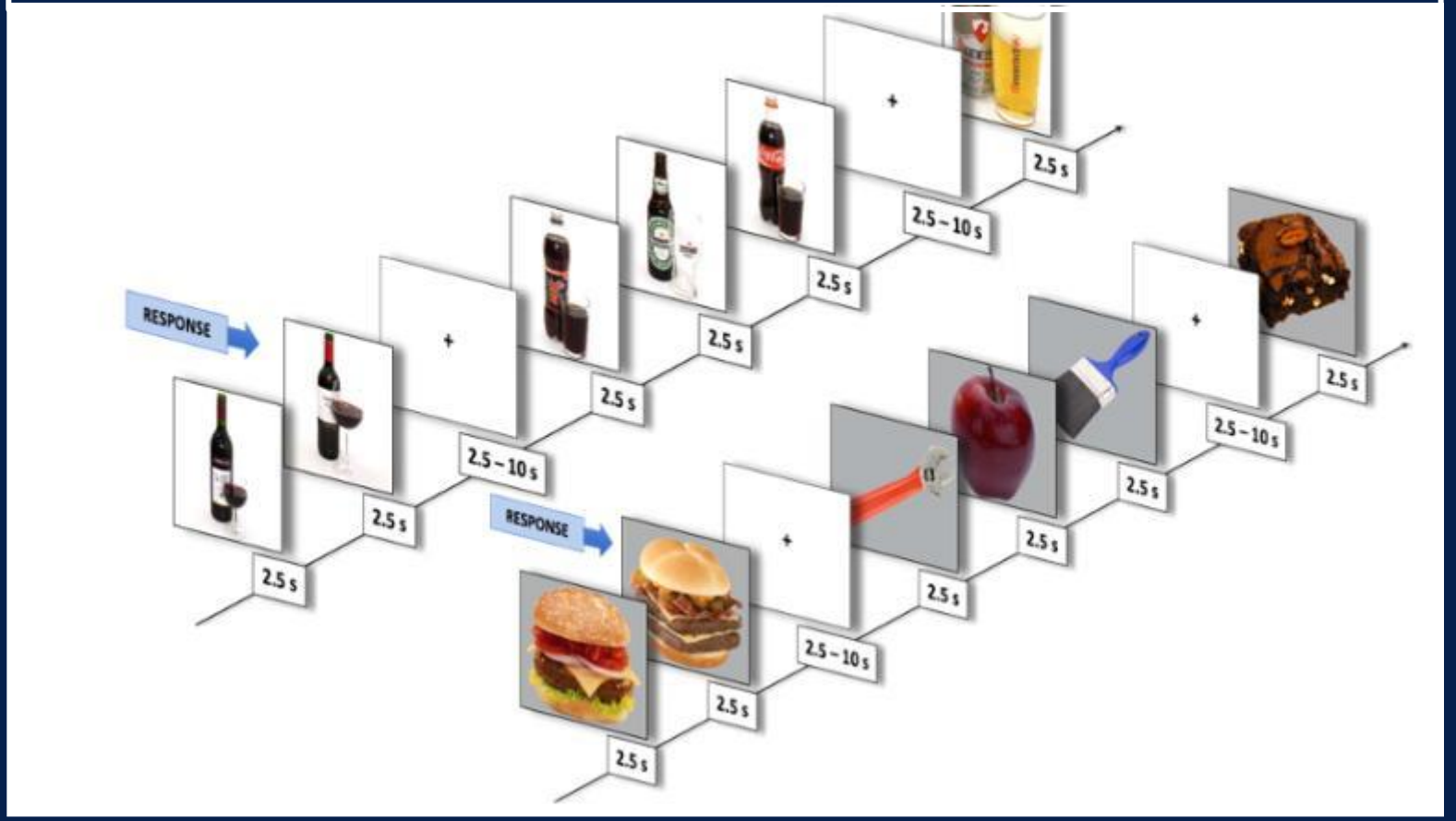
Cue Reactivity in the Mock Bar

Brain Functional MRI





Cue Reactivity Task



Demographics of Enrolled Patients

Characteristic	STAR-B (n=45)	Hendershot *et al.* (n=48)
Male Sex	21 (46.7%)	14 (29.1%)
Age <40 and ≥65	21 (46.7%), 4 (8.9%)	NR, 0 (0.0%)
Race/Ethnicity (Black, White)	17B (37.8%) 22W (48.9%)	7B (14.6%), 39W (81.2%)
Sexuality	3 Homo + 3 Bi (13.3%)	NR
*Body Mass Index Mean (range)	32.4 (23.7-49.0)	32.1
Comorbid Cannabis Use/Disorder	19 (42.2%), 13 former	NR (allowed mild CUD)
Comorbid Tobacco Use Disorder	15 (33.3%), 19 former	13 (27.1%)
Comorbid Depression/Anxiety	31 (68.9%)	NR but not exclusionary
Significant but Stable Medical Comorbidity (but not diabetes)	23 (51.1%) 1 CAD, 3 CKD, 13 FLD, 4 MH	NR but not necessarily exclusionary

Demographics of Enrolled Patients

Characteristic	STAR-B (n=45)	Hendershot *et al.* (n=48)
Severe AUD (6-11 DSM-5 criteria)	24 (53.3%)	NR, but avg. 4.2 sx
Mean Drinks Per Day STAR: 28-Day TLFB UNC: 30-Day TLFB	4.50 (31.5/week)	2.9 (20.3/week)
Mean Heavy Drinking Days >42g (♀) or >56g (♂) EtOH/day	12.7	9.1
*High Weekly Alcohol Drinking STAR: >14 (♀) or 21 (♂) drinks/week UNC: # drinks/drinking day	40 (88.9%)	NR

Current Status of STAR-B Trial (n=45)

Status	Number of Patients
Completed Trial (27 weeks): Target n=52	23 (22 @ 2.4 mg, 1 @ 1.7 mg)
Completed Dosing (20 weeks), in Follow-Up	4 (all @ 2.4 mg)
Medical Withdrawals	4 (at 0 mg x2, 1.0 mg and 1.7 mg)
Patient Withdrawals	2 (at 0.5 mg and 2.4 mg)
Currently Dosing 2.4 mg (max obesity maintenance dose) 1.7 mg (first obesity maintenance dose) 1.0 mg (DM dose, max STAR-T dose) 0.5 mg (max tested UNC trial dose) 0.25 mg	12 (includes enrolled pts only) 2 2 3 2 3

Adverse Events (AEs) We Have Seen

- Primarily GI, not generally severe, none serious
  - GERD, belching, bloating, flatulence, nausea, vomiting, diarrhea, constipation, abdominal cramping
  - Can usually be controlled with OTC meds and behavioral changes
- Other reported AEs
  - Const: fatigue, feeling less motivated to perform activities
  - Injection Site: bruising, pain
  - Psych: claustrophobia/panic attack in MRI, “vivid dreams”
  - Neuro: headaches, dizziness/lightheadedness
- Addiction-Specific Effects
  - Craving during cue reactivity
  - Decreased food, alcohol, and other drug consumption

Adverse Events (AEs) We Have Not Seen

- Serious GI complications
  - Acute pancreatitis (although we have seen asymptomatic bumps in liver tests and lipase)
  - Gastroparesis, bowel obstruction, other surgical emergencies
- Other addiction-specific effects or AEs of possible concern
  - Const: weight loss to the point of malnutrition
  - General: worsening of stable chronic conditions (CAD, FLD, CKD)
  - Psych: worsening depression, anxiety, SI/SA
  - Rebound increase in drinking during the post-dosing F/U phase

Comment

https://doi.org/10.1038/s41591-023-02634-8

GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders

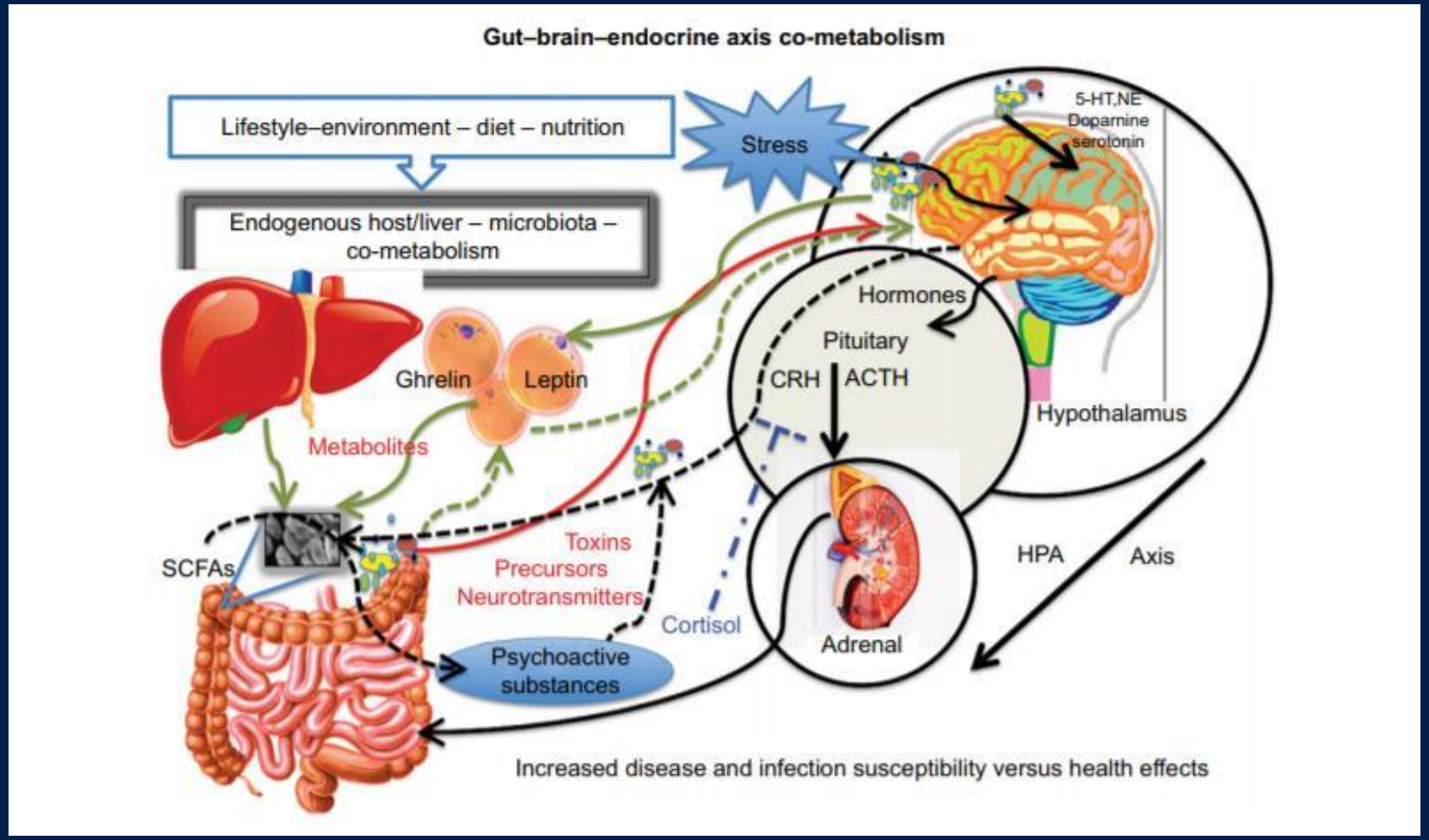
Lorenzo Leggio, Christian S. Hendershot, Mehdi Farokhnia, Anders Fink-Jensen, Mette Kruse Klausen, Joseph P. Schacht & W. Kyle Simmons

Preclinical and initial human studies suggest that glucagon-like peptide-1 receptor agonists may be promising treatments for alcohol use disorder, but existing approved treatments should be used until safety and efficacy is demonstrated in clinical trials.

The development and rapid clinical adoption of potent and long-lasting glucagon-like peptide-1 receptor agonists (GLP-1RAs) is quickly changing the landscape of diabetes and obesity treatment. In particular, semaglutide (marketed as Ozempic, Wegovy and Rybelsus) has attracted attention among the general public for its

Leggio, L., *et al. Nat Med* **29**, 2993–2995 (2023). https://doi.org/10.1038/s41591-023-02634-8

The Brain Does Not Function in Isolation



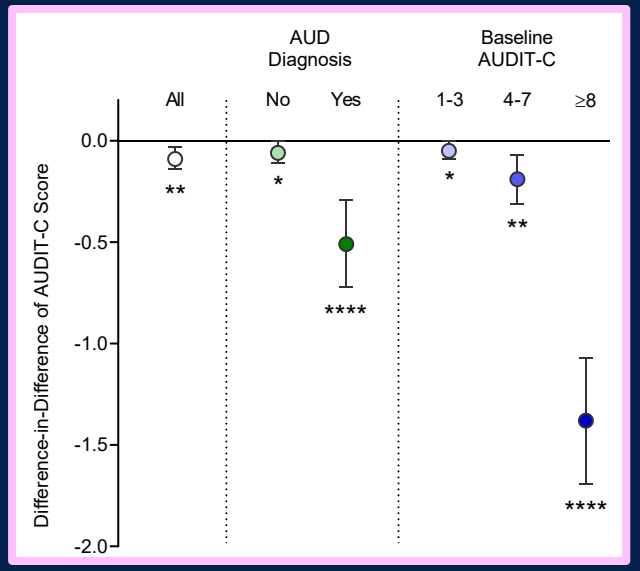
Obrenovich *et al.* Pathology and Laboratory Medicine International (2017) 22 : 21-30.

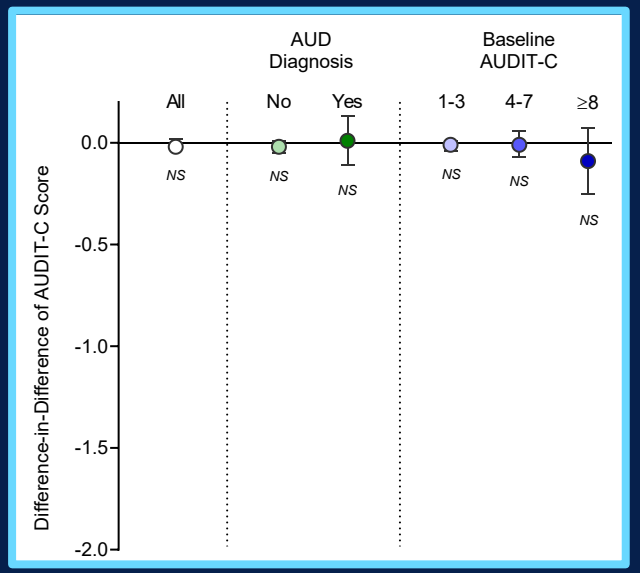
Final Takeaways/Summary

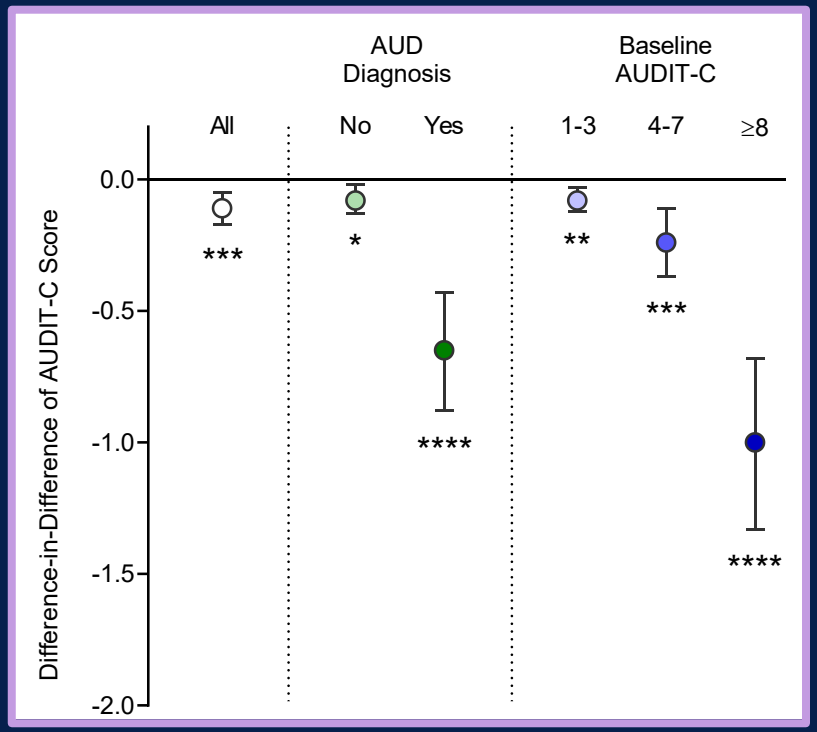
- GLP-1 Receptor Agonists (GLP-1RAs) have a unique mechanism of action that may be effective in helping patients with SUDs decrease craving and control their alcohol or drug use.
- “MAY be effective” does not mean “definitely WILL be effective!”
- Along with awaiting the results of ongoing clinical trials of GLP-1RA safety and efficacy in patients with addictions, plans to provide equitable access to these drugs must be considered.

What about trying DPP-4 Inhibitors?

- Retrospective cohort analysis of data from Veterans Aging Cohort Study
- Propensity score matching analysis evaluating AUDIT score and AUD diagnosis
  - Received GLP-1RA (n=14,130) vs. none (12,398)
  - Received DPP-4I (n=44,498) vs. none (n=40,938)
  - Received GLP-1RA (n=11,863) vs. DPP-4I (n=11,145)







Manuscript in preparation (M. Farokhnia et al).