



ASAM
ANNUAL CONFERENCE
Innovations in Addiction Medicine and Science
April 24-27, 2025 | Denver, CO

Early Clinical Signals On Repurposing GLP-1 Receptor Agonists for Alcohol Use Disorder



Disclosure Information

Stephanie T. Weiss, MD, PhD, MS

- No relevant financial relationships
- 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.

Session Learning Objectives

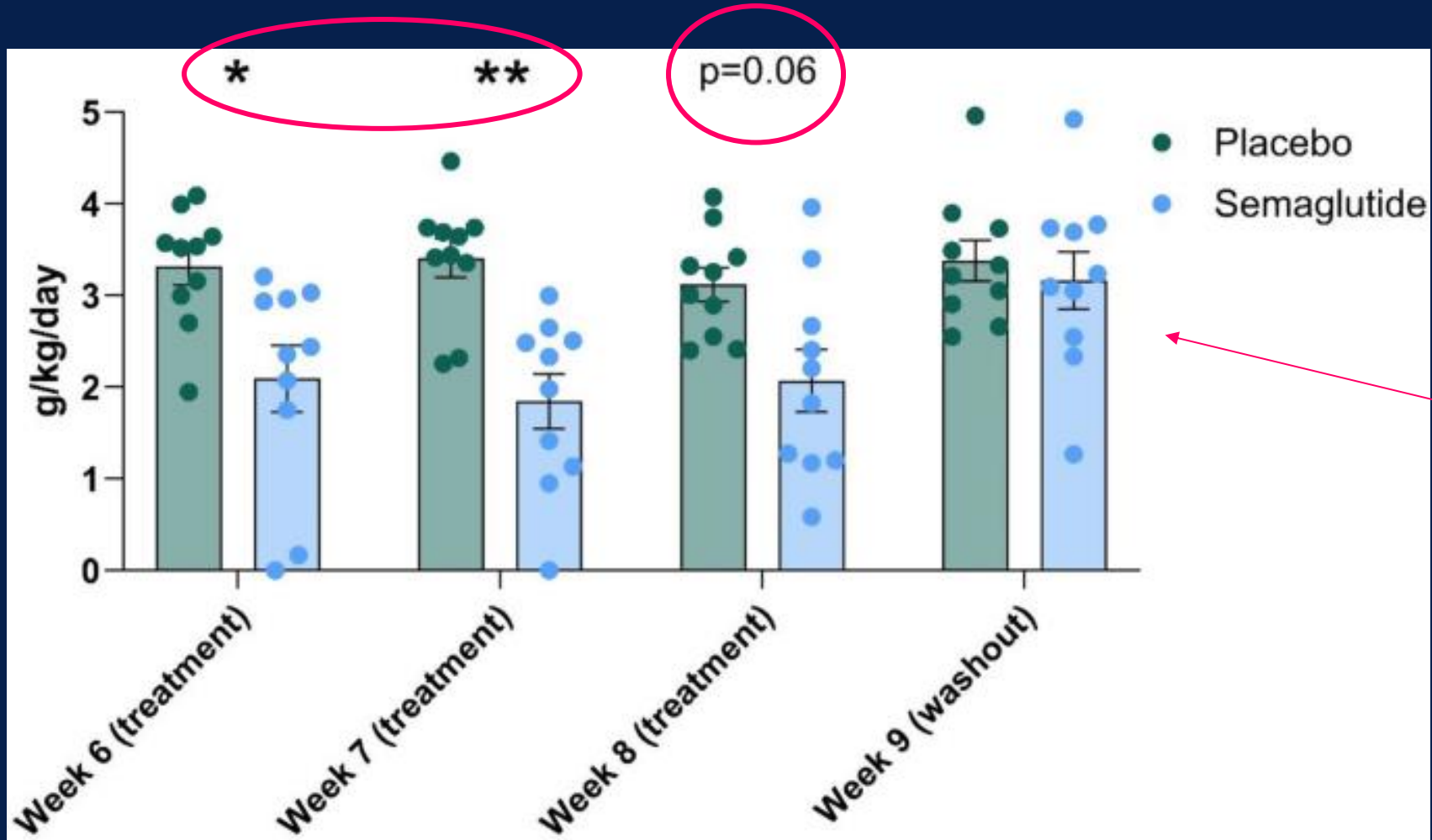
- 01 | Examine preclinical data supporting the use of GLP-1 receptor agonists (GLP-1RAs) for the treatment of alcohol use disorder (AUD).
- 02 | Analyze randomized clinical trials studying the safety and efficacy of GLP-1 receptor agonists (GLP-1RAs) for AUD.
- 03 | Identify common and rare adverse effects of manufactured semaglutide formulations.

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

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

Semaglutide Administration Decreased Alcohol Drinking in Alcohol-Preferring Vervet Monkeys



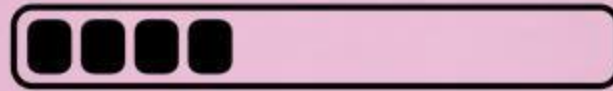
No significant difference in drinking in the week after the drug was stopped.

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

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

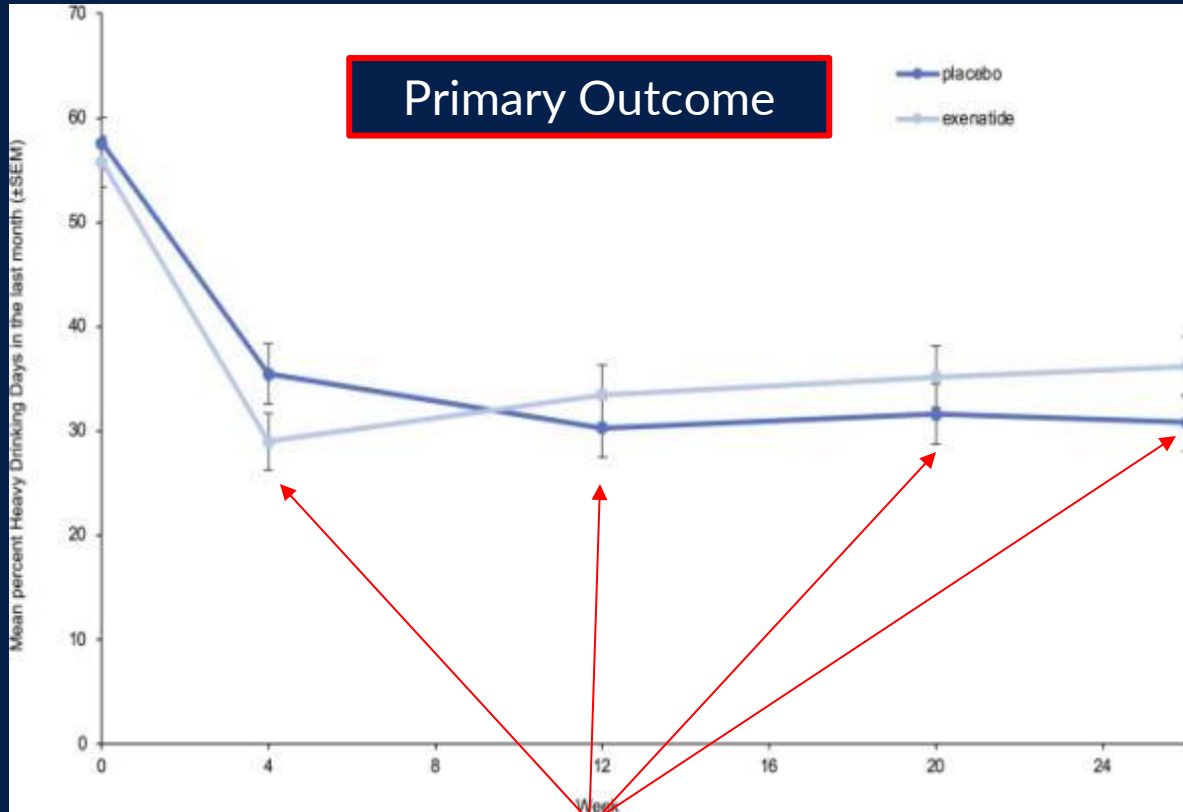
These observational and large-data studies in humans are suggestive of GLP-1RA efficacy for treating AUD, and they provide additional support for testing these compounds as treatments for AUD, but they cannot substitute for rigorous human randomized controlled trials.

Alcohol Loading

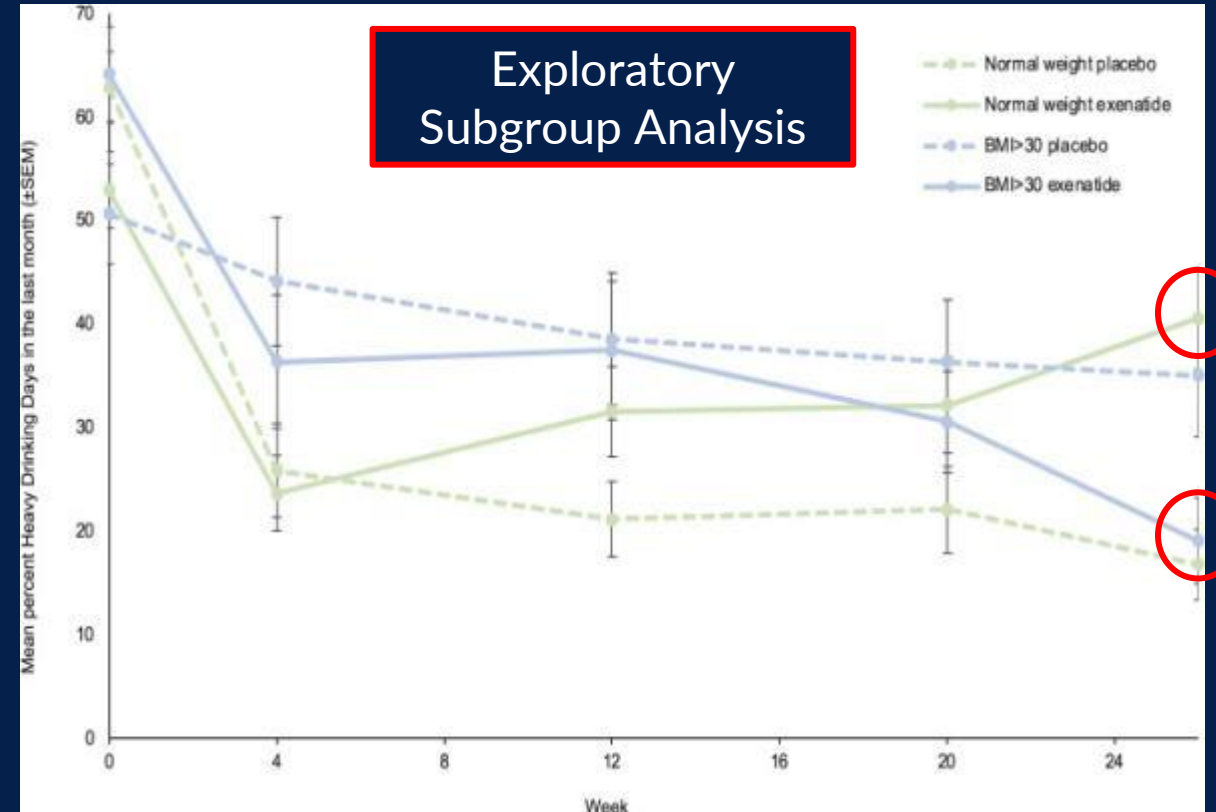


Please Wait.

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)

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Completed ⓘ

Semaglutide for Alcohol Use Disorder

ClinicalTrials.gov ID ⓘ NCT05520775

Sponsor ⓘ University of North Carolina, Chapel Hill

Information provided by ⓘ University of North Carolina, Chapel Hill (Responsible Party)

Last Update Posted ⓘ 2024-08-15



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Study Overview

Brief Summary

This is an early-Phase II human laboratory trial using a randomized, placebo-controlled, dose-ranging design to investigate the effects of semaglutide, a GLP-1 receptor agonist, on alcohol-related outcomes in adults with alcohol use disorder (AUD).

Detailed Description

This is an early-Phase II human laboratory trial using a randomized, placebo-controlled, dose-ranging design to investigate the effects of semaglutide, a GLP-1 receptor agonist, on laboratory alcohol responses and consumption, naturalistic alcohol consumption, and weight loss in participants with alcohol use disorder (AUD). Participants will attend weekly visits while semaglutide dosage is increased to 1.0mg over a period of approximately 9-10 weeks. Participants will attend weekly visits for medication

Study Start (Actual) ⓘ

2022-09-02

Primary Completion (Actual) ⓘ

2024-04-12

Study Completion (Actual) ⓘ

2024-04-19

Enrollment (Actual) ⓘ

48

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

FDA-approved for DM + CKD in 01/2025!

Summary of Semaglutide AUD Trials

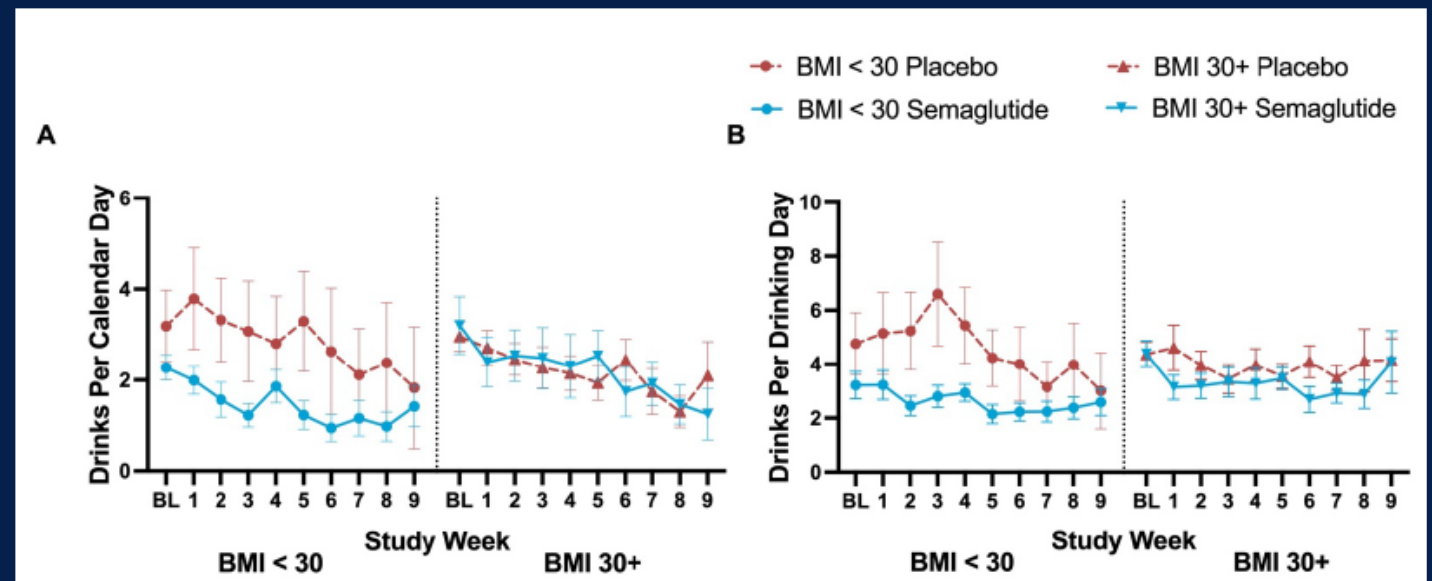
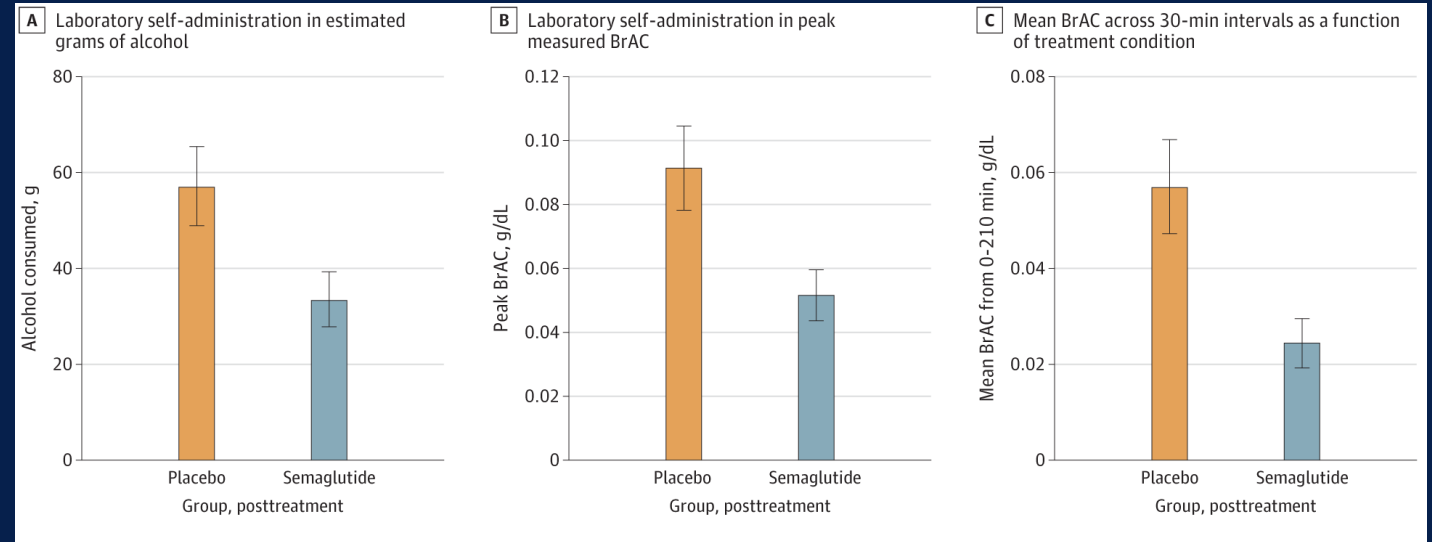
Study Location	SAUD (UNC-NC)	SEMALCO (Denmark)	Rybelsus (CU-CO)	STAR-T (OSU-OK)	STAR-B (NIDA-MD)
Enrollment	48	108	50	80	52
Drug Form	Injectable	Wegovy	Rybelsus	Injectable	Injectable
Max Dose	1.0 mg	2.4 mg	7 mg	1 mg	2.4 mg
Dosing	9 weeks	26 weeks	8 weeks	12 weeks	20 weeks
Primary Outcome	BrAC, alcohol 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)	Currently enrolling	Currently enrolling	Currently enrolling

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. Bremner, 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%)

Semaglutide Therapy for Alcohol Reduction (STAR)

Two Harmonized RCTs

Oklahoma State University

NIDA IRP/TAMB

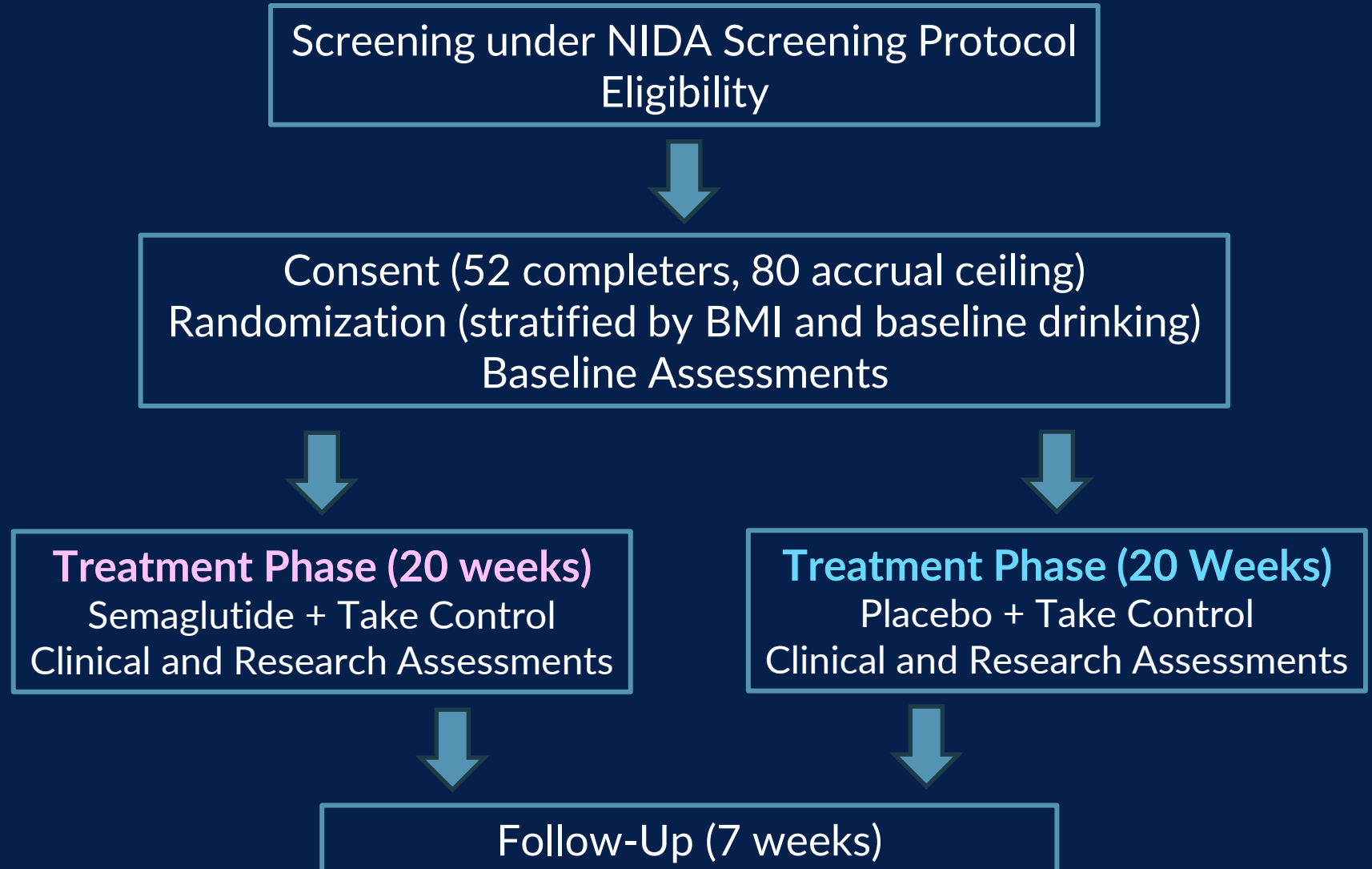


NCT05891587
PI: W. Kyle Simmons

NCT06015893
PI: Lorenzo Leggio

Schema for STAR-B

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



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>

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)

Demographics of Enrolled Patients

Characteristic	STAR-B (n=37)	Hendershot <i>et al.</i> (n=48)
Male Sex	19 (51.4%)	14 (29.1%)
Age <40 and >65	16 (43.2%), 3 (8.1%)	NR, 0 (0.0%)
Race/Ethnicity (Black, White)	16B (43.2%) 16W (43.2%)	7B (14.6%), 39W (81.2%)
Sexuality	3 Homo + 2 Bi (13.5%)	NR
*Body Mass Index Mean (range)	33.2 (25.4-49)	32.1
Comorbid Cannabis Use/Disorder	17 (46.0%), 9 former	NR (allowed mild CUD)
Comorbid Tobacco Use Disorder	12 (32.4%), 17 former	13 (27.1%)
Comorbid Depression/Anxiety	25 (67.6%)	NR but not exclusionary
Significant but Stable Medical Comorbidity (but not diabetes)	15 (40.0%) 1 CAD, 2 CKD, 9 FLD, 3 MH	NR but not necessarily exclusionary

Demographics of Enrolled Patients

Characteristic	STAR-B (n=37)	Hendershot <i>et al.</i> (n=48)
Severe AUD (6-11 DSM-5 criteria)	21 (56.8%)	NR, but avg. 4.2 sx
Mean Drinks Per Day STAR: 28-Day TLFB UNC: 30-Day TLFB	4.69 (32.8/week)	2.9 (20.3/week)
Mean Heavy Drinking Days >42g (♀) or >56g (♂) EtOH/day	13.1	9.1
*High Weekly Alcohol Drinking STAR: >14 (♀) or 21 (♂) drinks/week UNC: # drinks/drinking day	33 (89.2%)	NR (2.9/day avg.)

Current Status of STAR-B Trial (n=37)

Status	Number of Patients
Completed Trial (27 weeks): Target n=52	18 (17 @ 2.4 mg, 1 @ 1.7 mg)
Completed Dosing (20 weeks), in Follow-Up	2 (both @ 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	11 (includes enrolled pts only)
2.4 mg (max obesity maintenance dose)	2
1.7 mg (first obesity maintenance dose)	4
1.0 mg (DM dose, max STAR-T dose)	1
0.5 mg (max tested UNC trial dose)	3
0.25 mg	1

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)
 - ◆ Psych: worsening depression, anxiety, SI/SA
 - ◆ Rebound increase in drinking during the post-dosing F/U phase

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

 Check for updates

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



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.