Semaglutide Circus: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists to Treat Addiction

Jeffrey Brent, M.D., Ph.D.

Stephanie T. Weiss, M.D., Ph.D., M.S.

Learning Objectives

1) Explain the pharmacology and toxicology of GLP-1 receptor agonists

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

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

4) Identify methods to provide fair and just access to new, expensive medications like GLP-1 receptor agonists to all segments of society

The Skinny on GLP-1 Receptor Agonists: The Good, the Bad, the Beautiful, and the Ugly

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Division of Pulmonary and Critical Care Medicine
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School of Medicine

No conflicts of interest to disclose

“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

How This Came to Be

- Approx 2 of 3 Americans are overweight or obese
- 2005: First Glucagon-like peptide-1 receptor agonist approved for the treatment of type II diabetes
- Social media, esp. Tik Tok, reported that people taking them were losing weight
- GLP-1R agonists then repurposed as wt loss drugs
- Half of US adults meet these criteria:

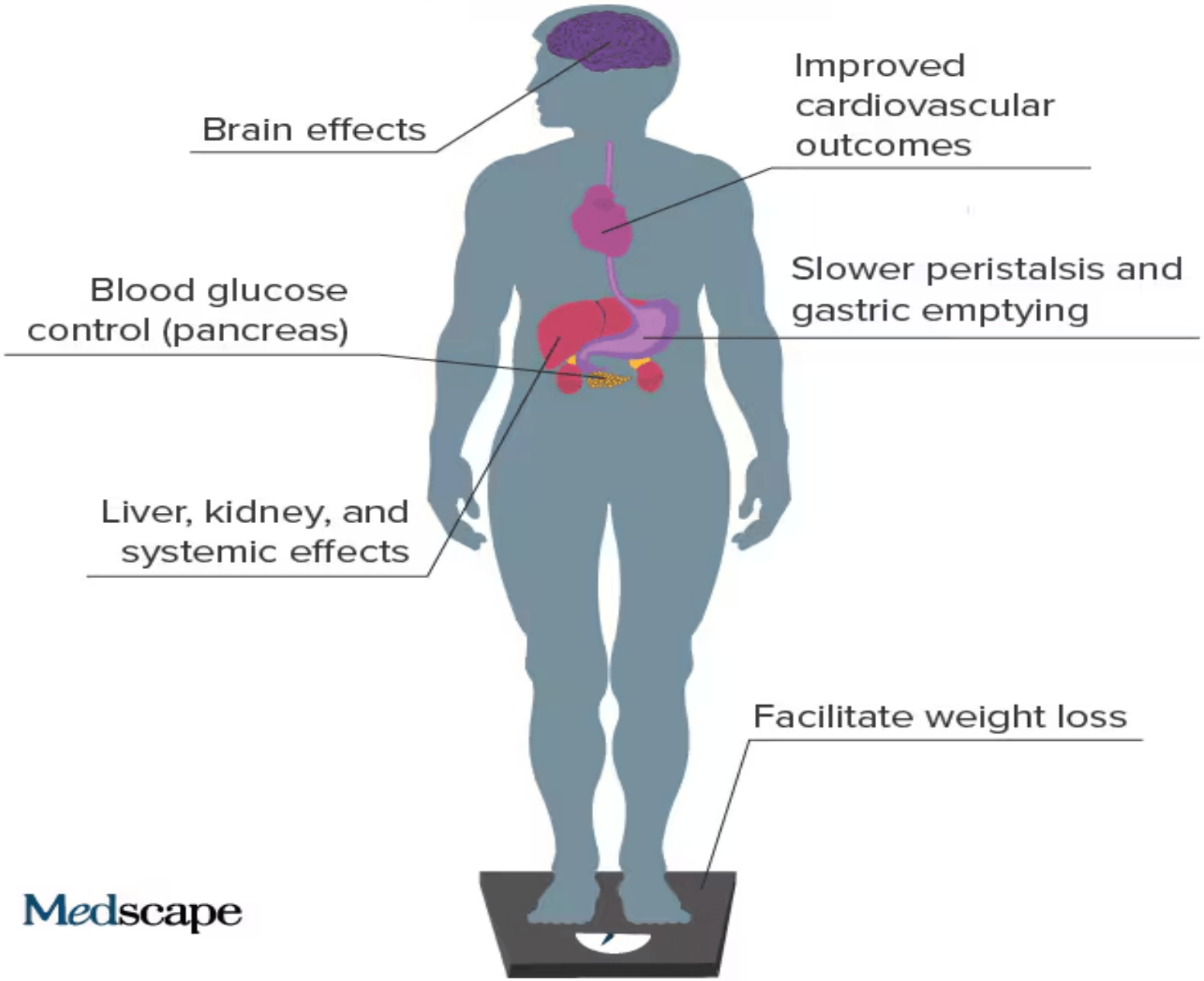
Box 1: US Food and Drug Administration indications for semaglutide

- Ozempic (injection) and Rybelsus (tablets) for diabetes
- Wegovy (injection) for obesity or overweight:
  - BMI ≥30 kg/m^2 or greater
  - BMI ≥27 kg/m^2 or greater plus at least one weight-related condition (high blood pressure, type 2 diabetes or high cholesterol)

Brown, BMJ , 2023

Where GLP-1s Work Now -- and What's Coming

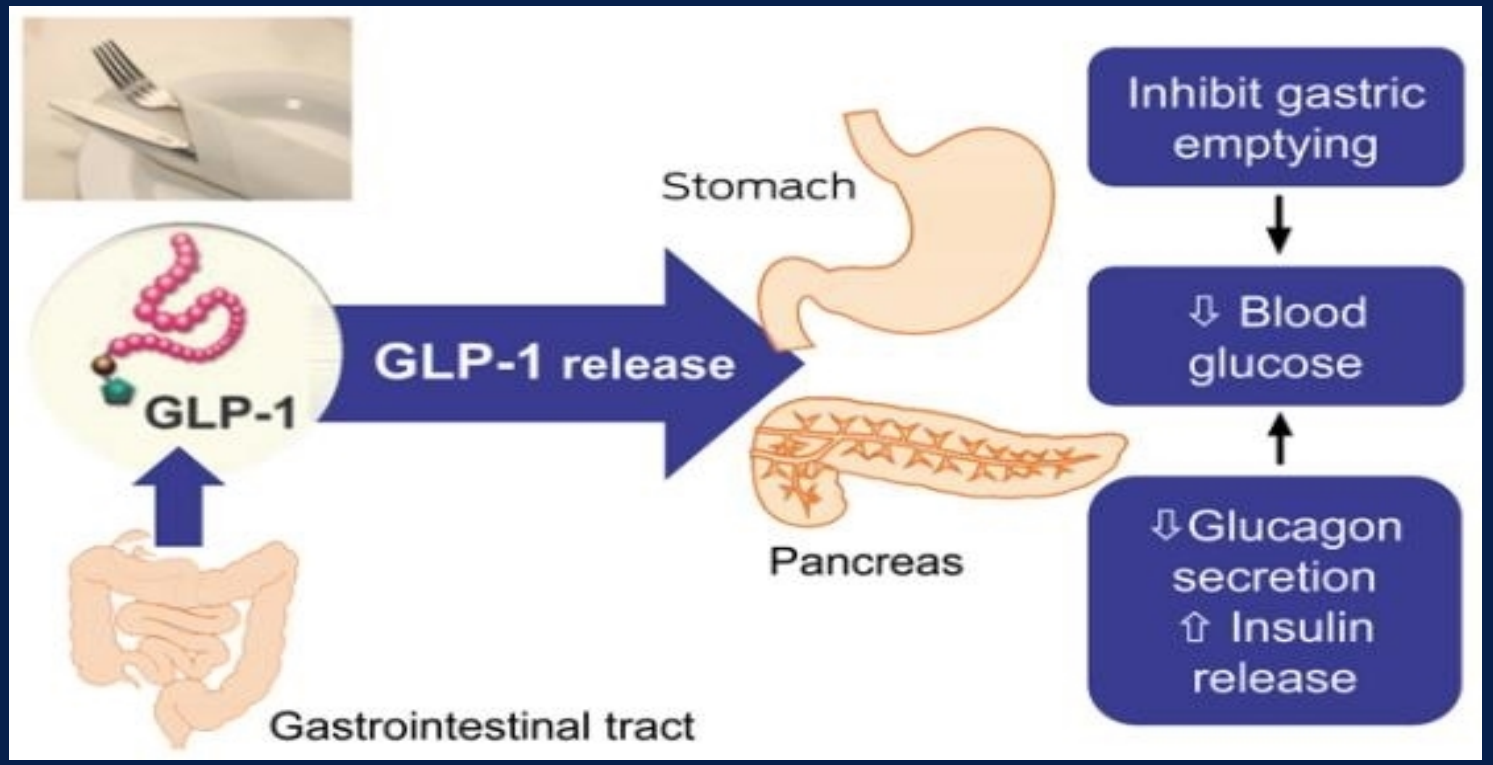
(Based on Evidence So Far)



Medscape

Glucagon-Like Peptide-1 (GLP-1)

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



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

Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis

Haiqiang Yao,[1,2] Anqi Zhang,[2] Delong Li,[1,2] Yuqi Wu,[1,2] Chong-Zhi Wang,[3,4] Jin-Yi Wan,[1,2] Chun-Su Yuan[3,4]

- 76 RCTs of 15 GLP-1RAs
- 39, 246 participants

YAO 2024 BMJ 2024;384:e076410

Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis

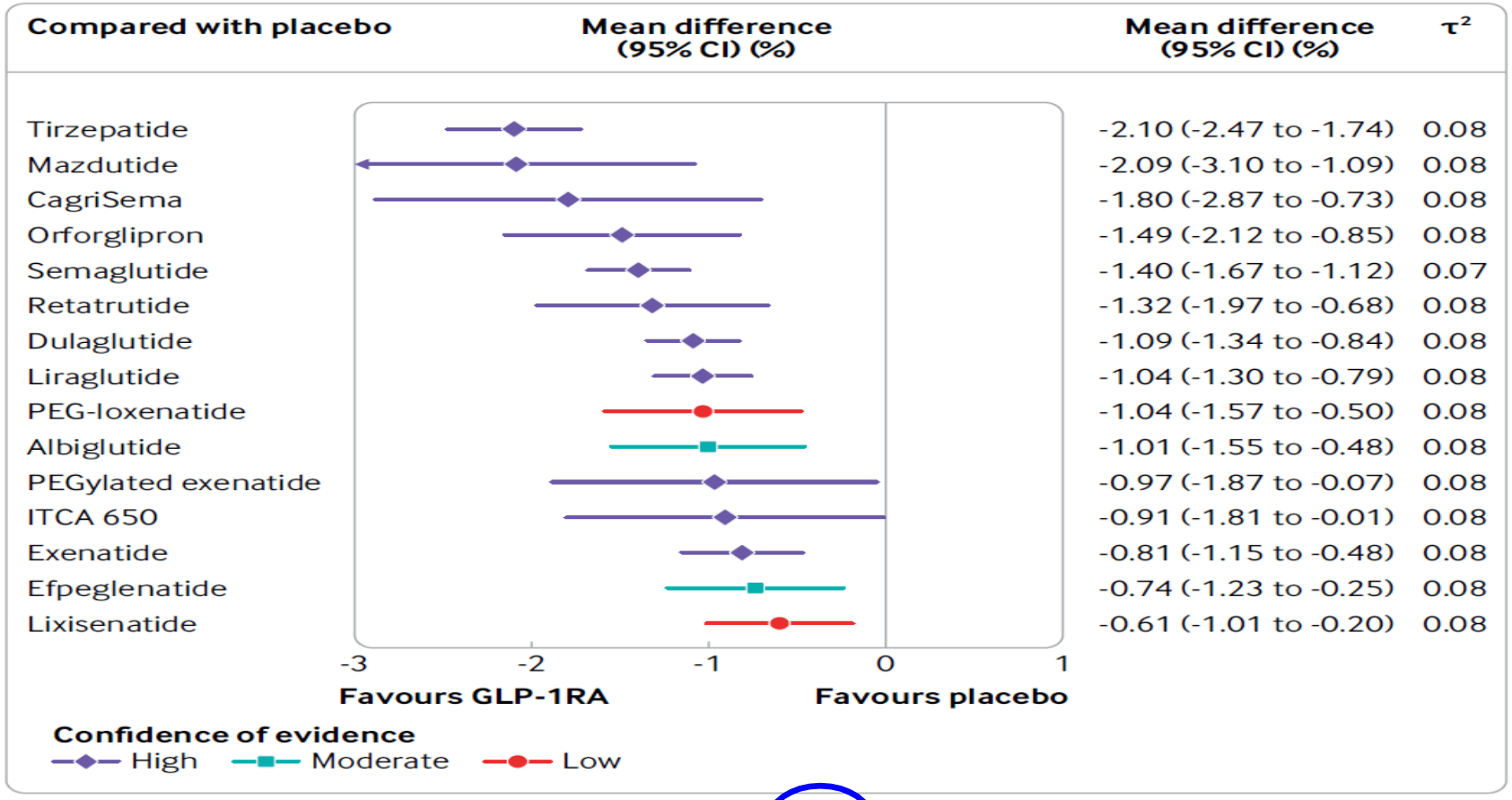


Fig 3 | Forest plot of network effect sizes between GLP-1RAs and placebo for HbA_{1c} measured in percentage. According to the network confidence meta-analysis (CINeMA) framework, the certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

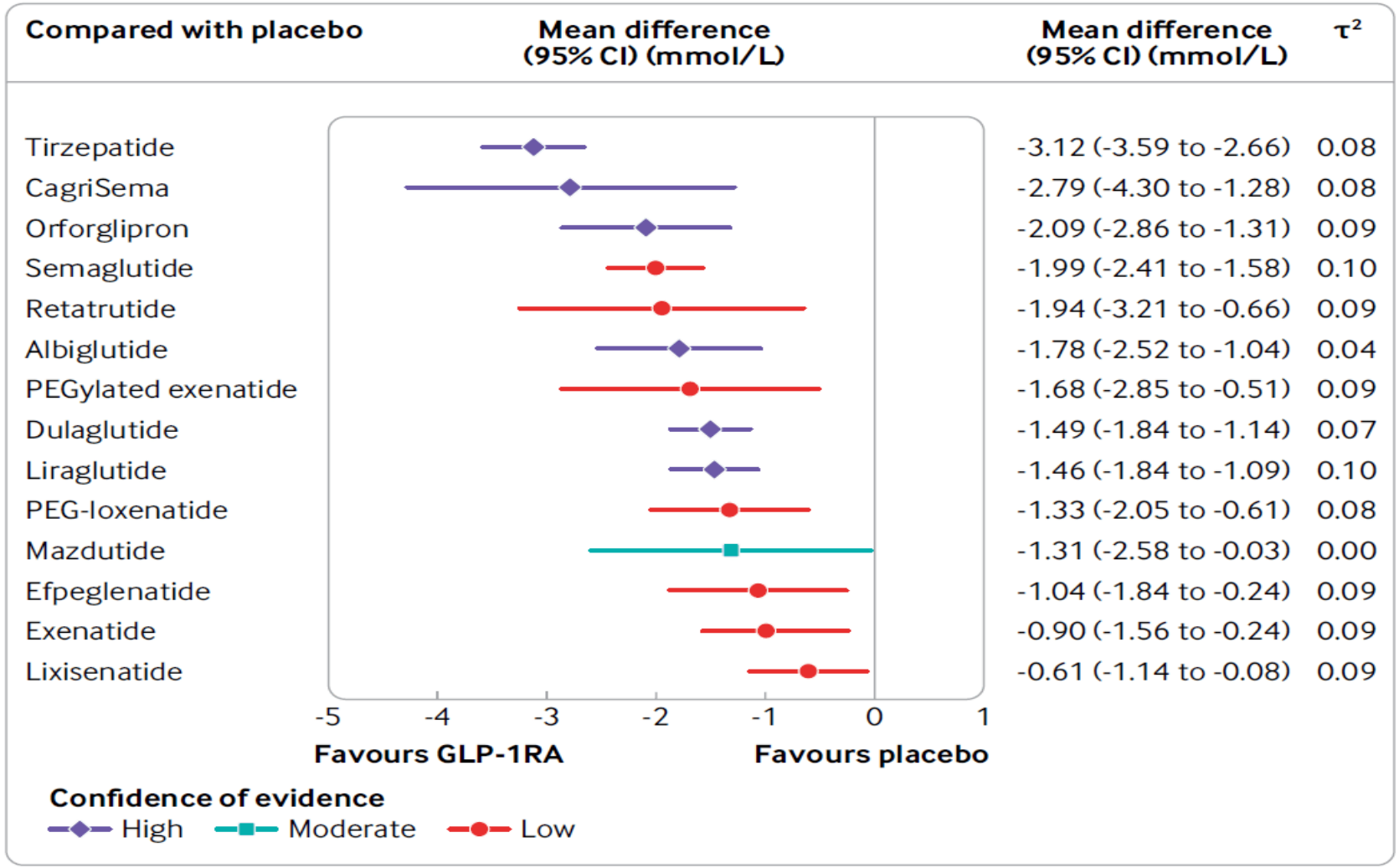


Fig 5 | Forest plot of network effect sizes between GLP-1RAs and placebo for fasting blood glucose. Certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide

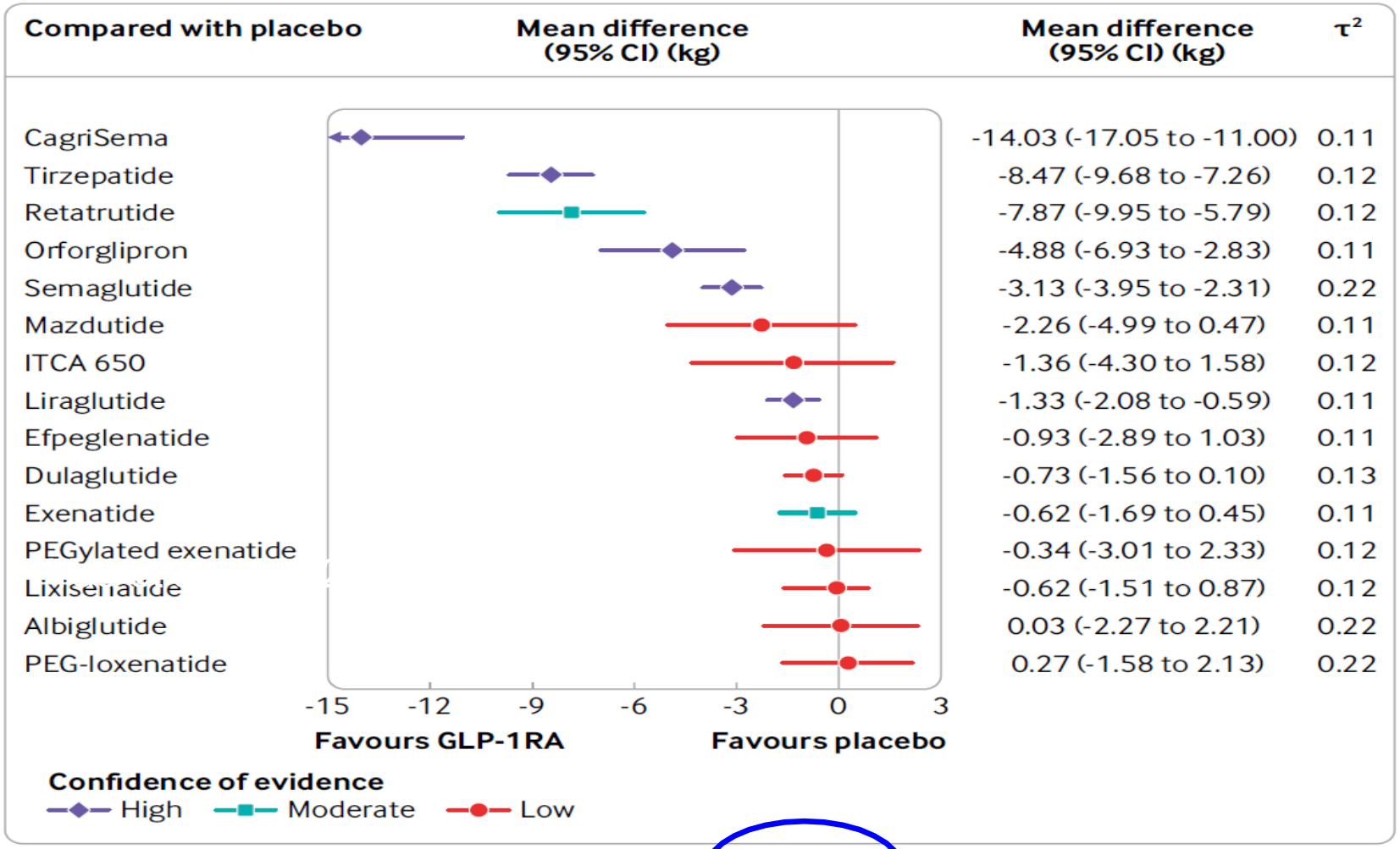


Fig 7 | Forest plot of network effect sizes between GLP-1RAs and placebo for weight loss. Certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

Yao et al., BMJ 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

RCT of 17,604 patients w/ a mean FU of 39.8 Months

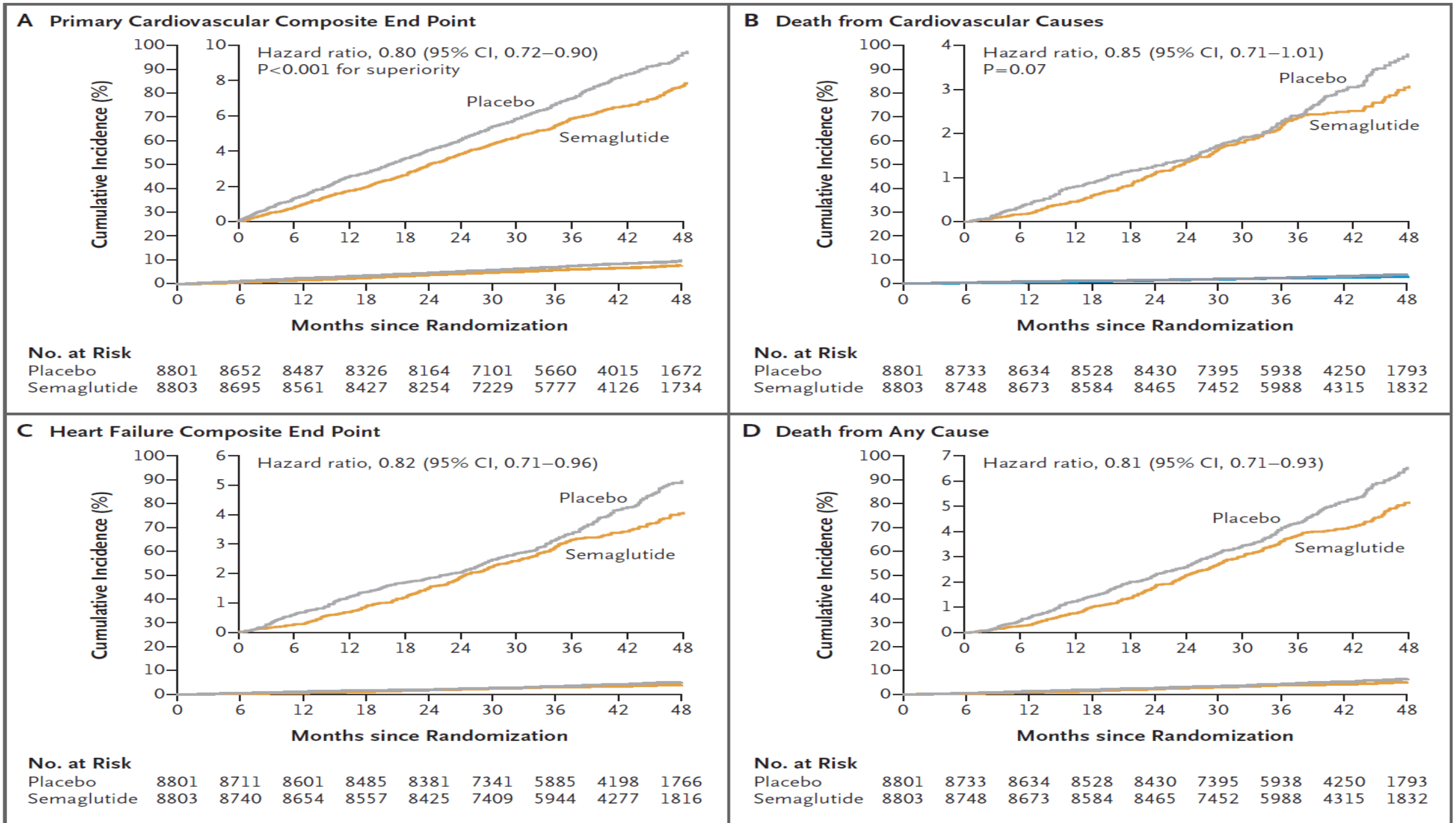

A Primary Cardiovascular Composite End Point
Hazard ratio, 0.80 (95% CI, 0.72–0.90)
P<0.001 for superiority
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8652 8487 8326 8164 7101 5660 4015 1672
Semaglutide 8803 8695 8561 8427 8254 7229 5777 4126 1734
B Death from Cardiovascular Causes
Hazard ratio, 0.85 (95% CI, 0.71–1.01)
P=0.07
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8733 8634 8528 8430 7395 5938 4250 1793
Semaglutide 8803 8748 8673 8584 8465 7452 5988 4315 1832
C Heart Failure Composite End Point
Hazard ratio, 0.82 (95% CI, 0.71–0.96)
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8711 8601 8485 8381 7341 5885 4198 1766
Semaglutide 8803 8740 8654 8557 8425 7409 5944 4277 1816
D Death from Any Cause
Hazard ratio, 0.81 (95% CI, 0.71–0.93)
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8733 8634 8528 8430 7395 5938 4250 1793
Semaglutide 8803 8748 8673 8584 8465 7452 5988 4315 1832

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N = 8803)	Placebo (N = 8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

JAMA Network | Open

Original Investigation | Pharmacy and Clinical Pharmacology

Glucagon-Like Peptide-1 Receptor Agonists and Pancreatic Cancer Risk in Patients With Type 2 Diabetes

Rachel Dankner, MD, MPH; Havi Murad, PhD; Nirit Agay, PhD; Liraz Olmer, MSc; Laurence S. Freedman, PhD

No increased risk of pancreatic cancer

RESEARCH LETTER

GLP-1 Receptor Agonists and Colorectal Cancer Risk in Drug-Naive Patients With Type 2 Diabetes, With and Without Overweight/Obesity

Wang et al, JAMA Oncology, 2024

Decreased rate of CRC with 15 yr FU

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

Stephanie T. Weiss, M.D., Ph.D., M.S.

Translational Addiction Medicine Branch
Intramural Research Program
National Institute on Drug Abuse
National Institutes of Health

- **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**

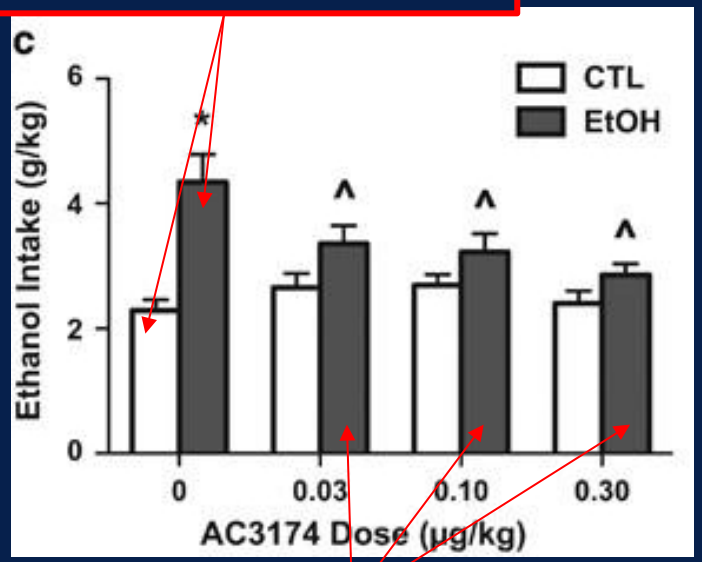
Over A Decade of Preclinical Evidence Supports a Role for GLP-1 in AUD

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

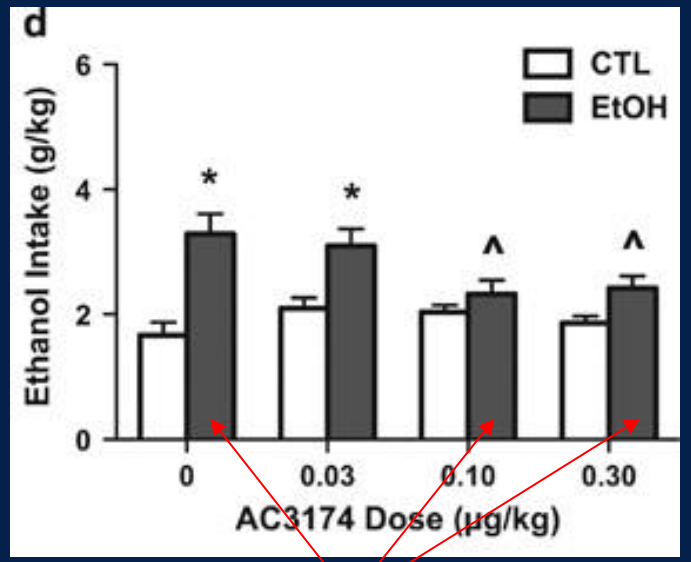
Administration of GLP-1 or GLP-1 agonists to rodents decreases drinking and attenuates the reinforcing properties of alcohol, suggesting that the GLP-1R is a potential target for treating AUD.

Effect of AC3174 (a GLP-1RA) in a Mouse Model of Alcohol Dependence

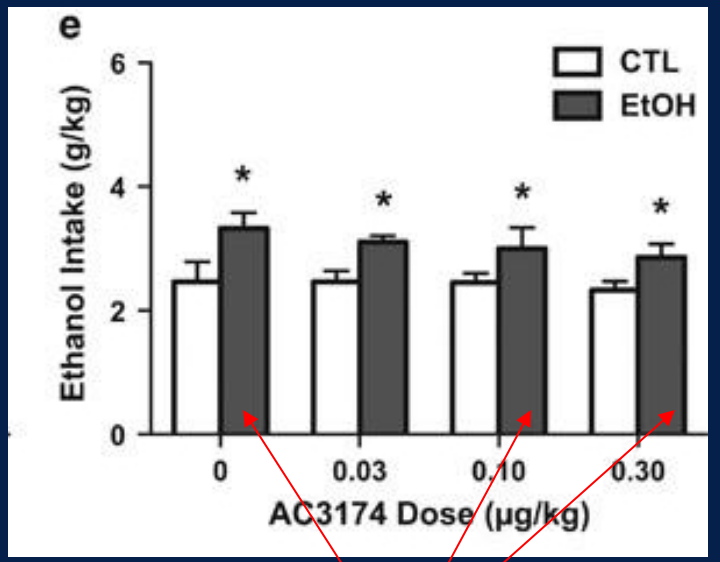
EtOH mice injected with vehicle consumed more alcohol than control mice



All doses of AC3174 significantly reduced drinking in EtOH but not control mice



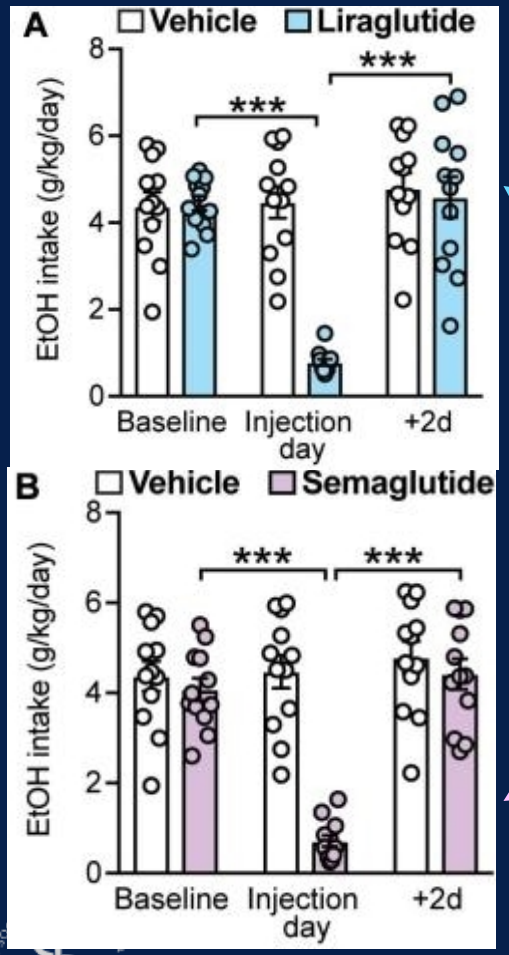
After 1 week washout, EtOH mice receiving the medium or high doses of AC3174 continued to drink significantly less alcohol vs. EtOH mice getting vehicle



This effect dissipated after a second week of washout

Suchankova, P., *et al.*, (2015). *Translational Psychiatry*, *5*(6): e583-e583.

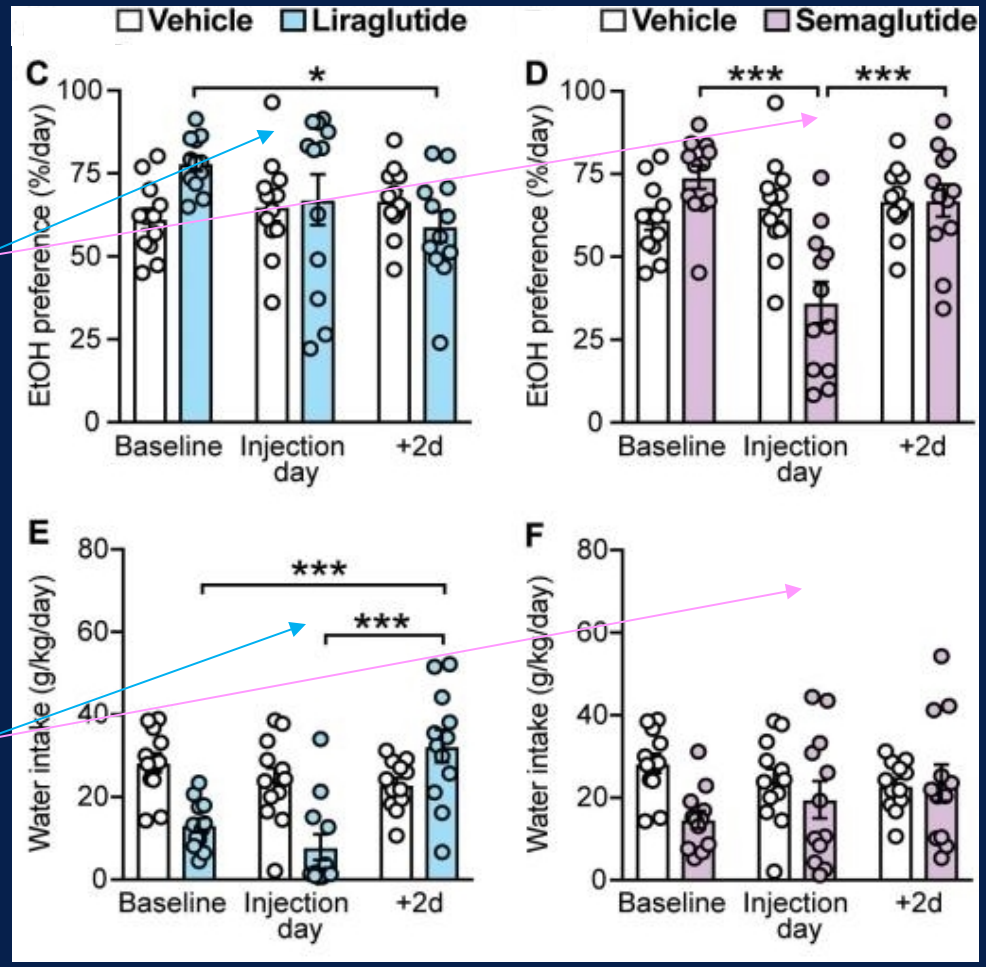
Intermittent Access 2-Bottle Choice Rat Study with Liraglutide and Semaglutide



Both liraglutide and semaglutide decreased EtOH intake

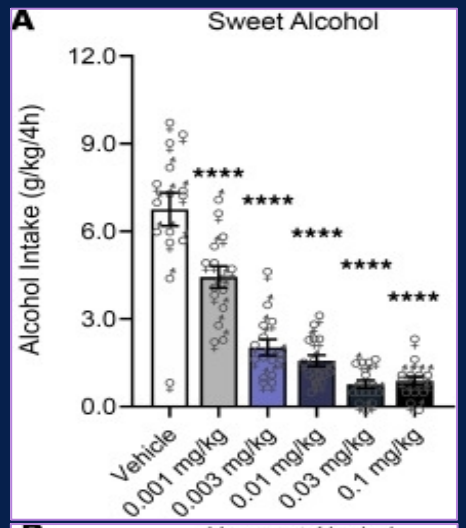
Both liraglutide and semaglutide decreased EtOH preference, but semaglutide decreased it more

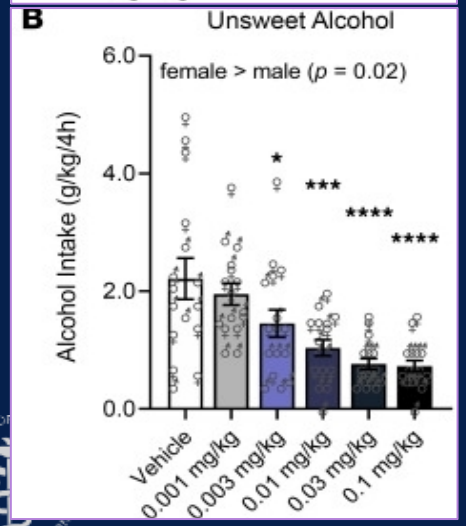
Liraglutide also nonspecifically decreased water intake, while semaglutide did not



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

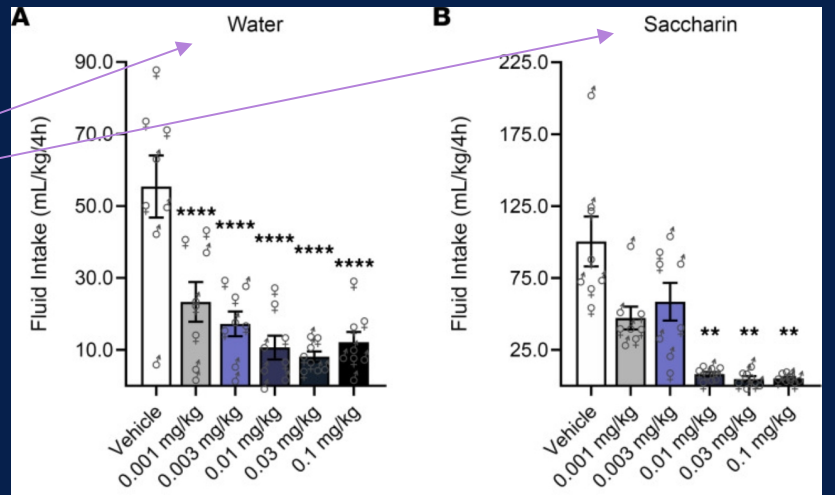
Semaglutide Dose-Dependently Reduces Binge-Like Drinking in Drinking-in-the-Dark Mice

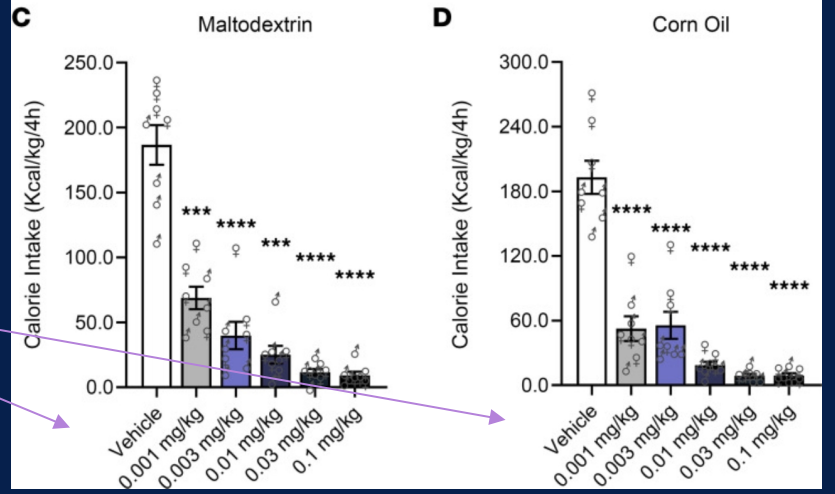




Both sweet and unsweet alcohol drinking were dose-dependently decreased

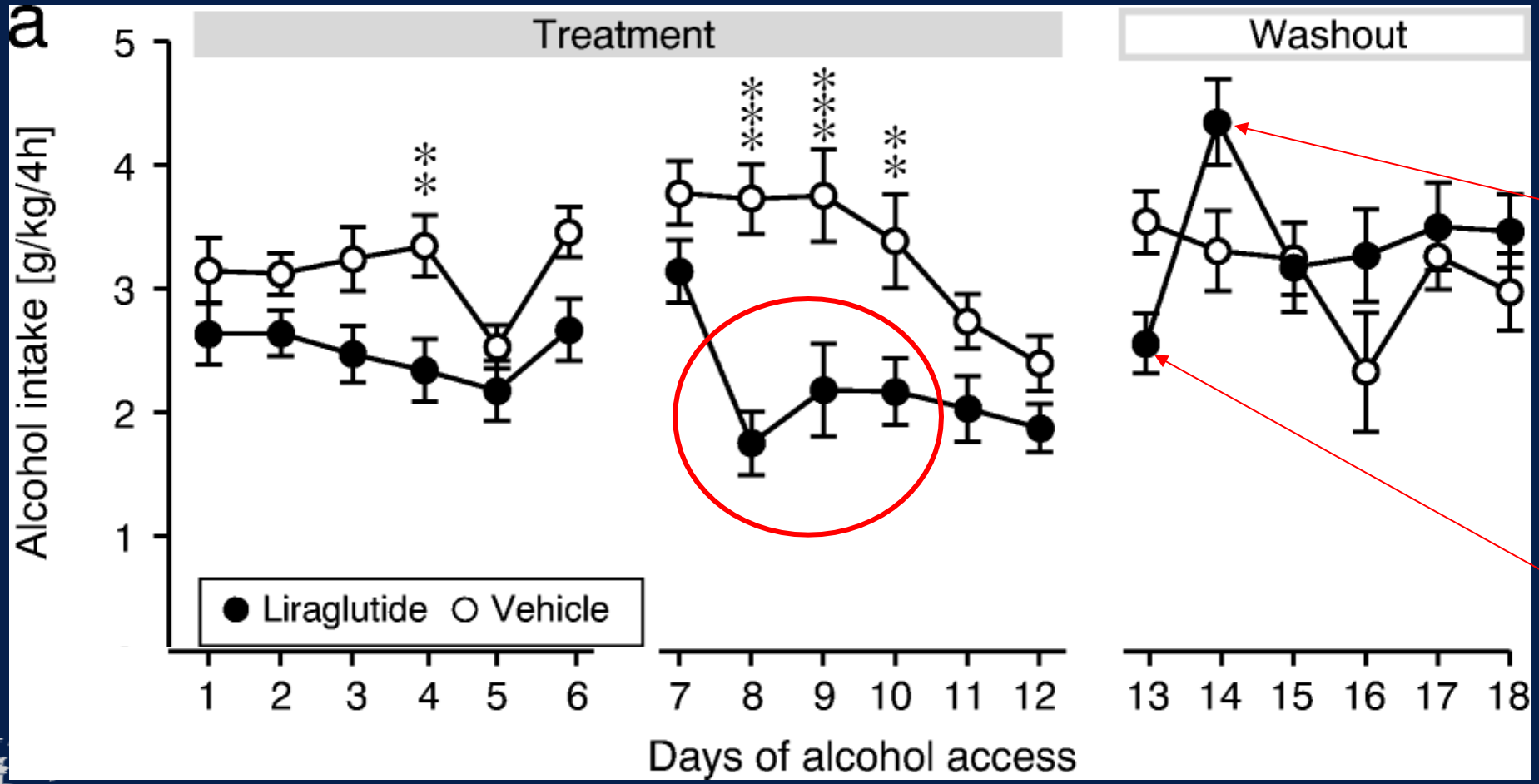
Semaglutide also decreased fluid intake, including water, a noncaloric sweet solution (saccharin), and two unsweet caloric solutions (maltodextrin and corn oil)





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

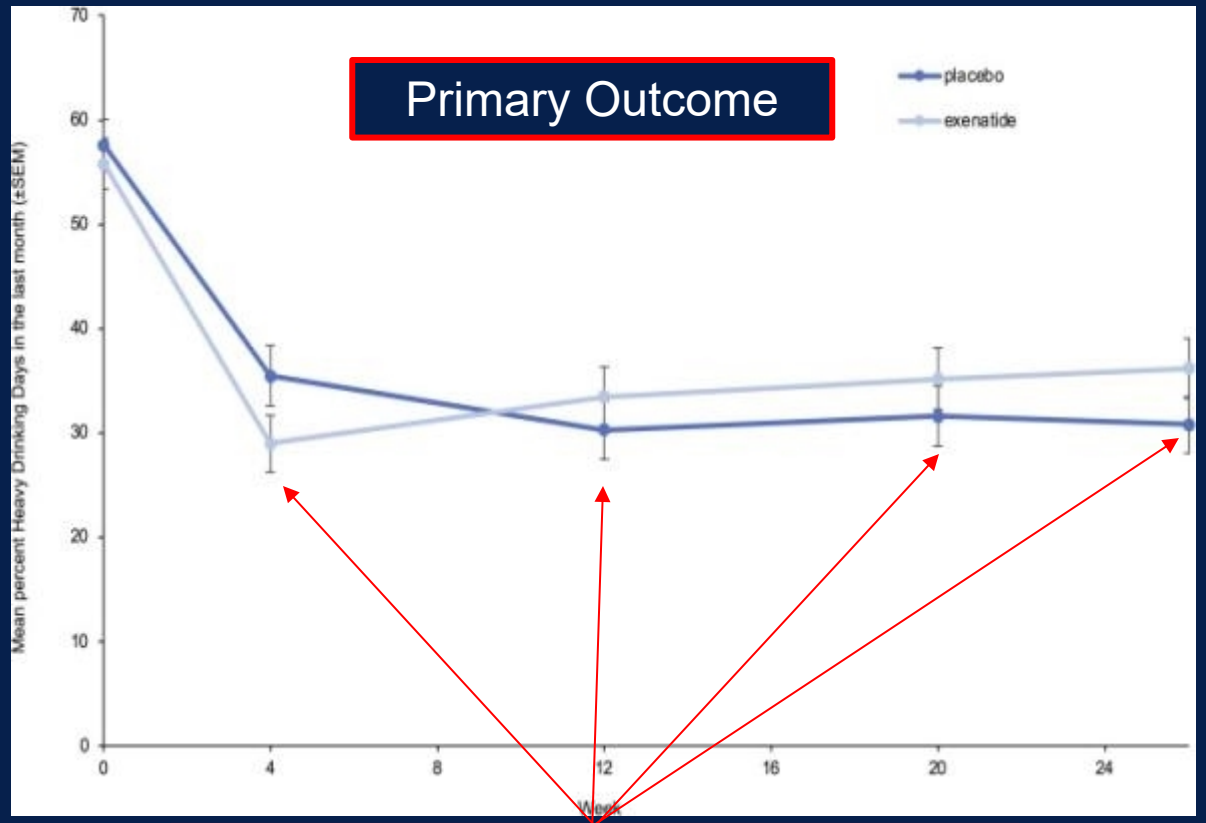
Thomsen, M., *et al.* (2019) *Psychopharmacology*, *236*: 603-611.

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

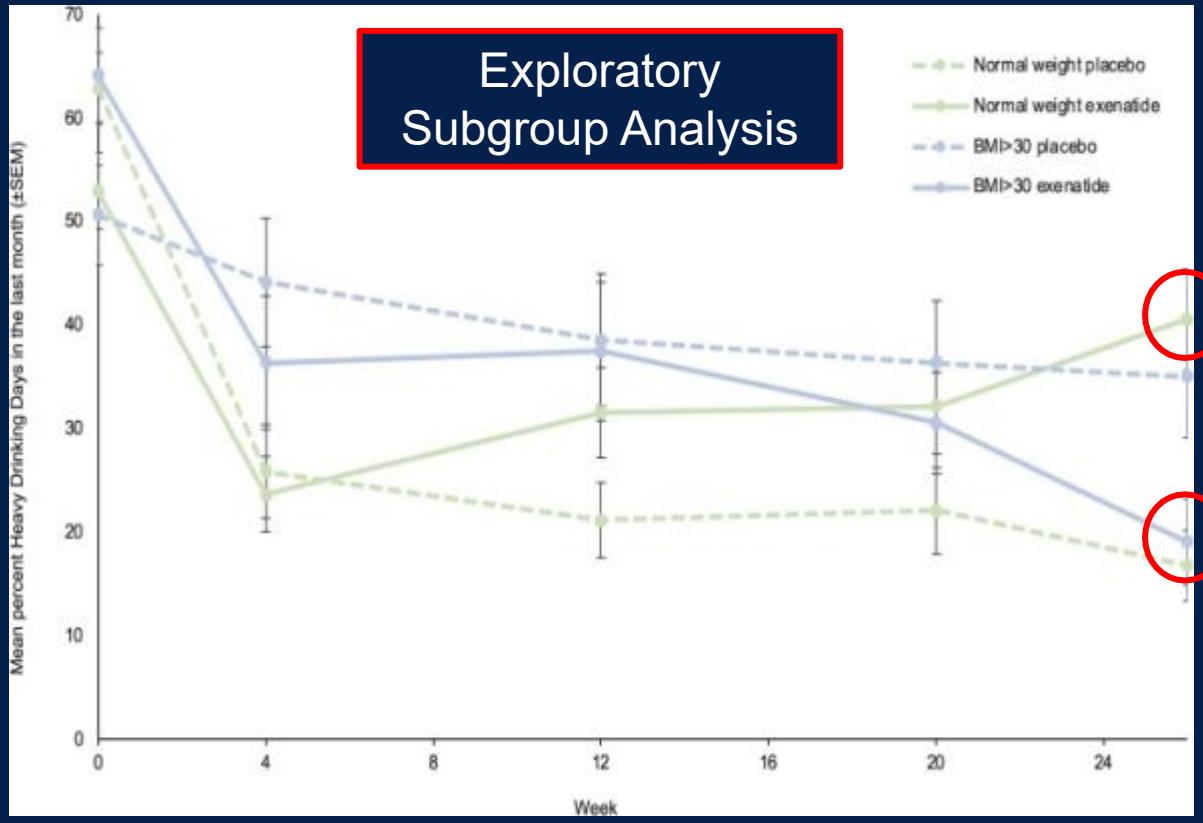
Study Reference	Findings
*Suchankova, ***Transl. Psychiatry*** (2015) 5: e583	Variation in *GLP1R* ass'd w/ AUD (genetic association study)
Wium-Anderson, ***Basic & Clin. Pharm. & Tox.*** (2022) 131: 372-379	GLP-1RA tx ass'd w/ lower risk of alcohol-related events (national registry cohort/case series)
*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 (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)

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.

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

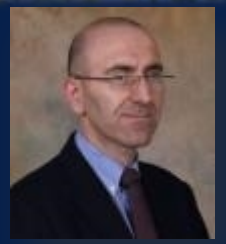
Semaglutide Therapy for Alcohol Reduction (STAR)

Two Harmonized RCTs

Oklahoma State University

PI: W. Kyle Simmons

NIDA IRP/TAMB



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

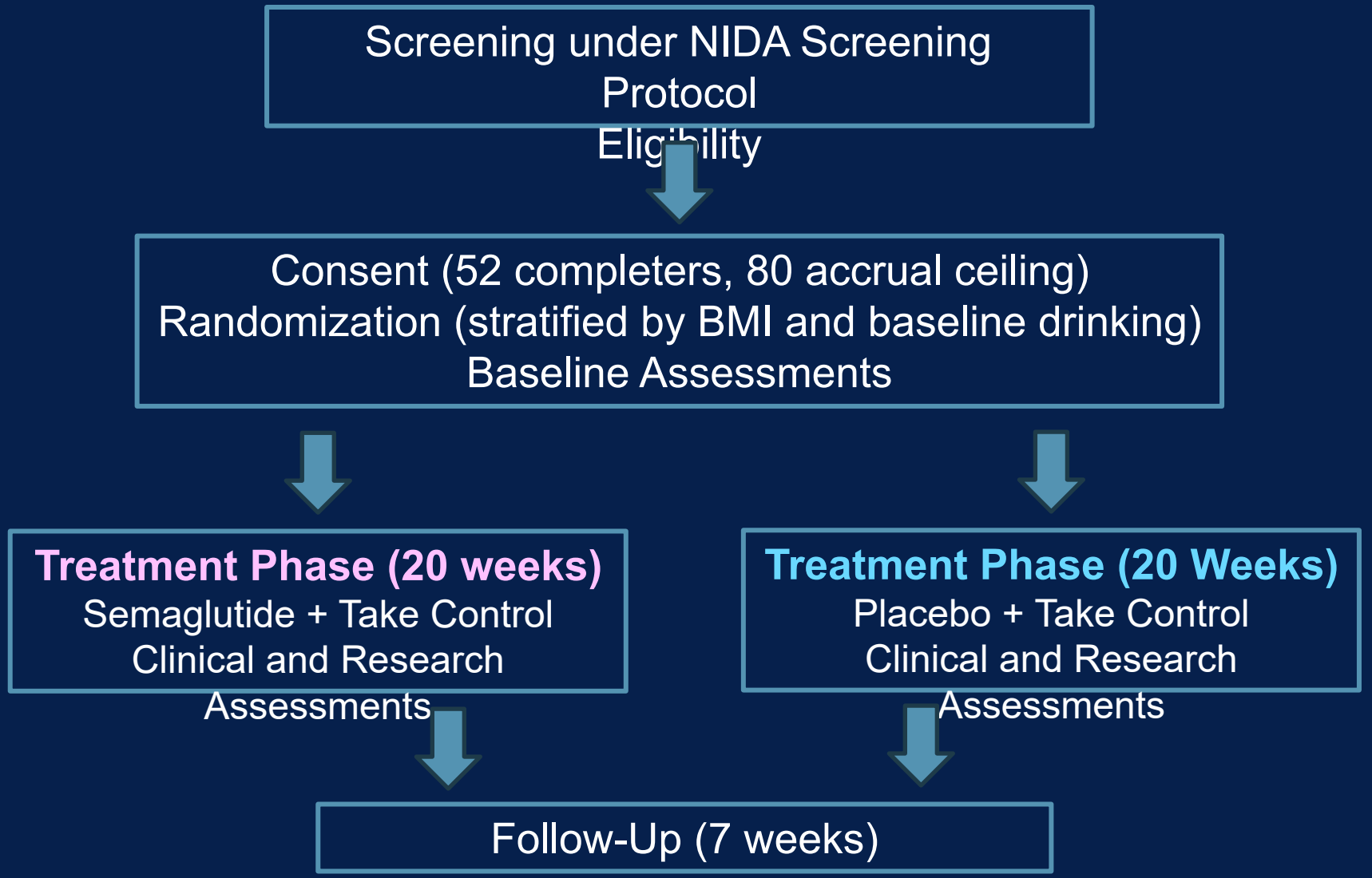
Primary Completion (Estimated)

2030-12-31

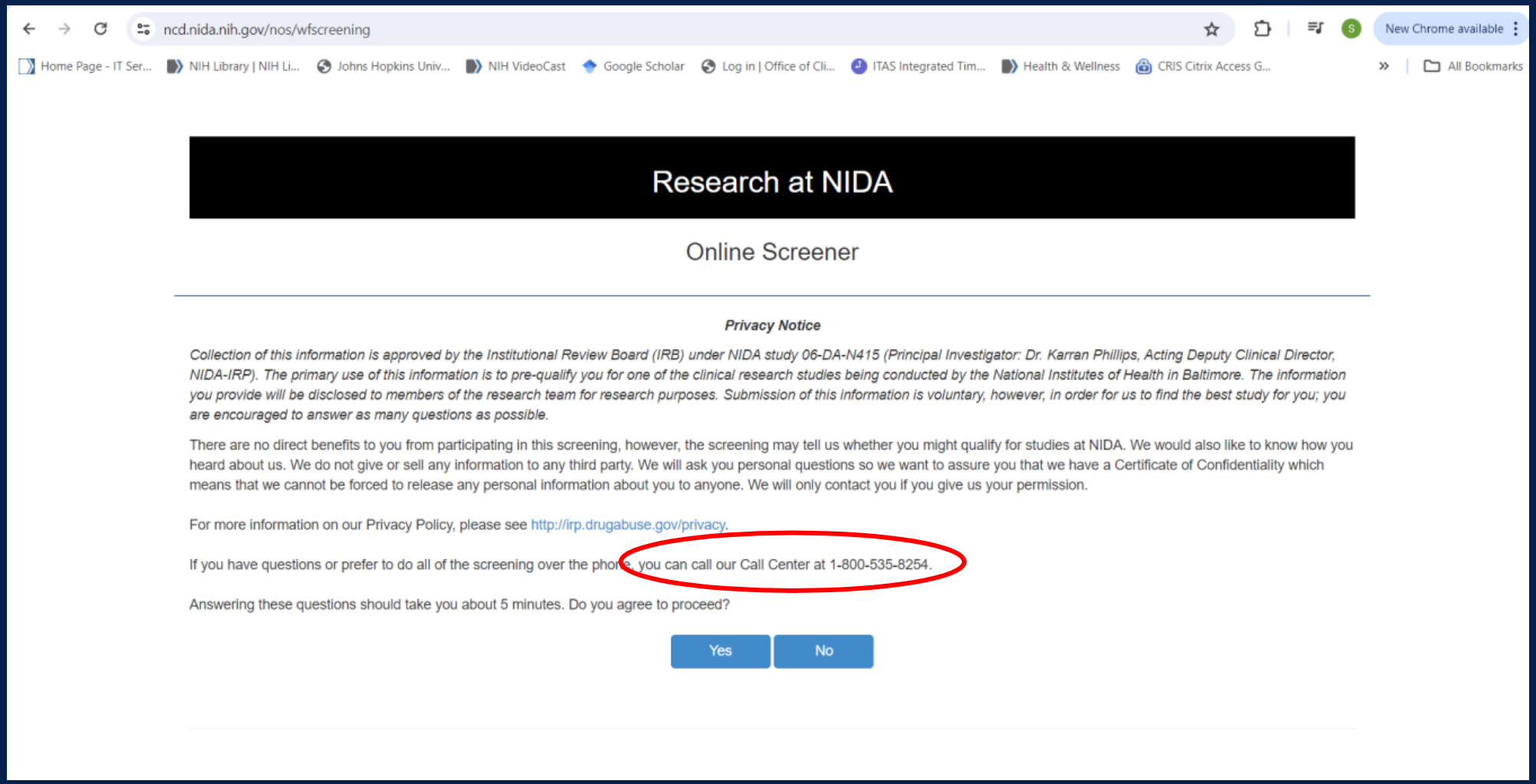
Study Completion (Estimated)

Schema for STAR-B

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



NIDA Intramural Research Program Screening



https://researchstudies.nida.nih.gov/before-continuing.html
https://ncd.nida.nih.gov/nos/wfscreening

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

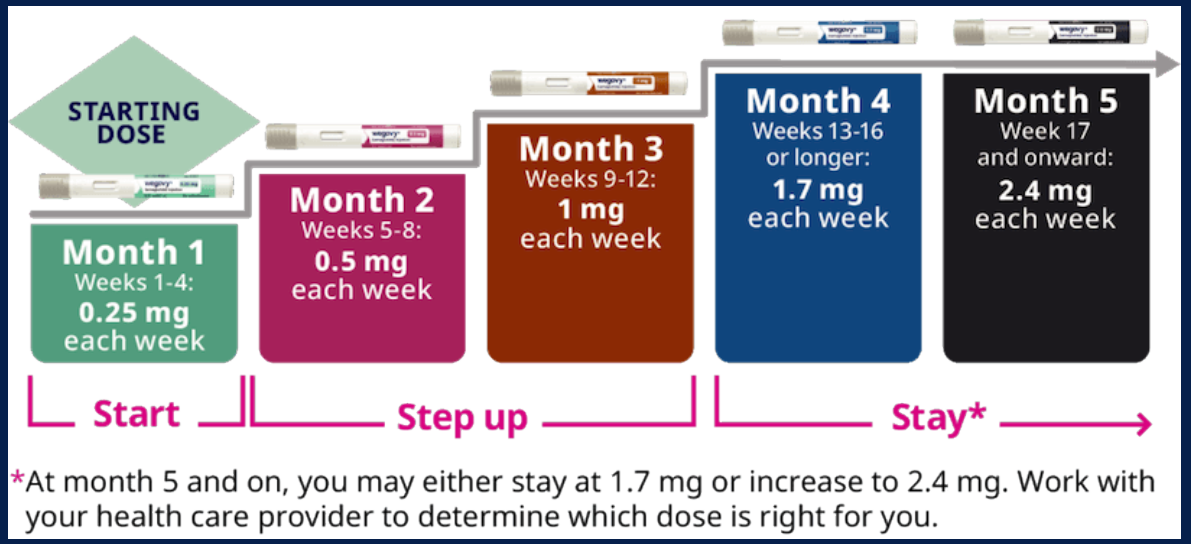
Exclusion

- Metabolic
  - BMI outside 25-50 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 Therapy for Alcohol Reduction (STAR)

Ozempic

FDA-approved for diabetes

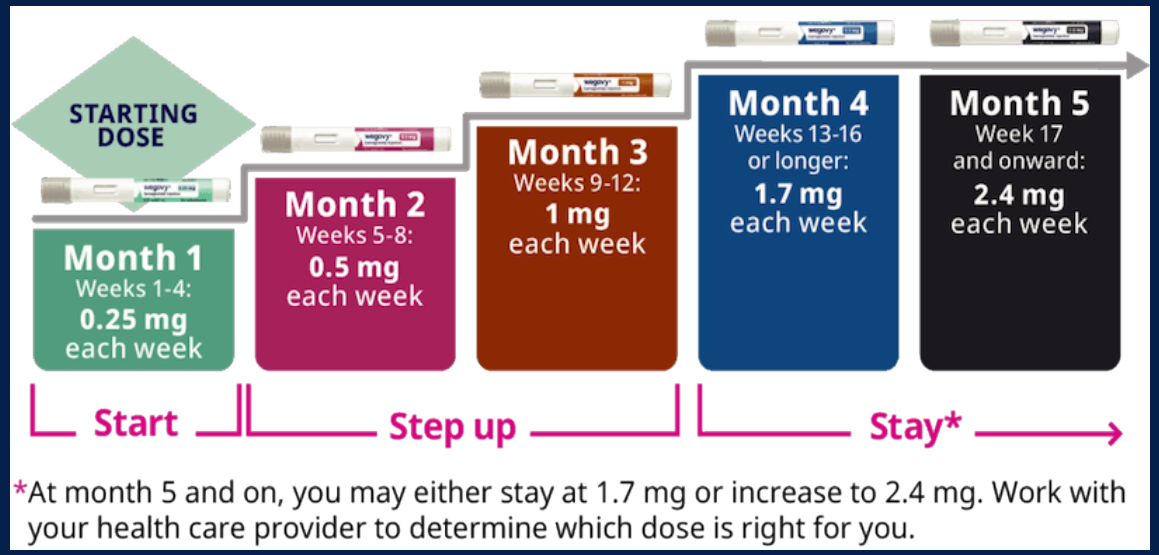
Wegovy

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

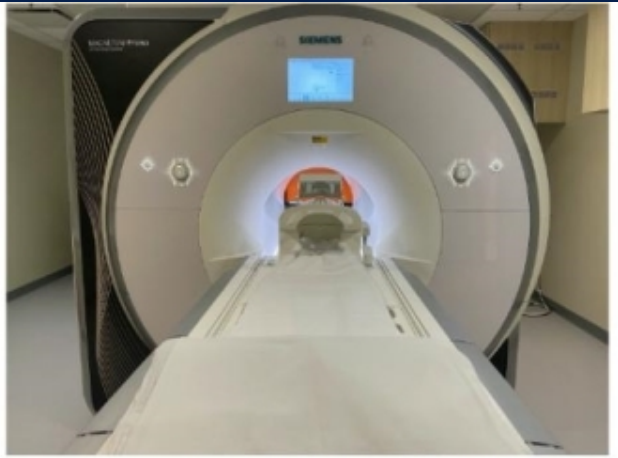
- **Other Drinking Outcomes**
  - Heavy drinking days
  - WHO drinking risk levels
  - Phosphatidylethanol (PEth) levels
- **Changes in Study Tasks**
  - Virtual Reality (Food Craving)
  - Cue Reactivity (Alcohol Craving)
  - Brain fMRI (resting, task-based)

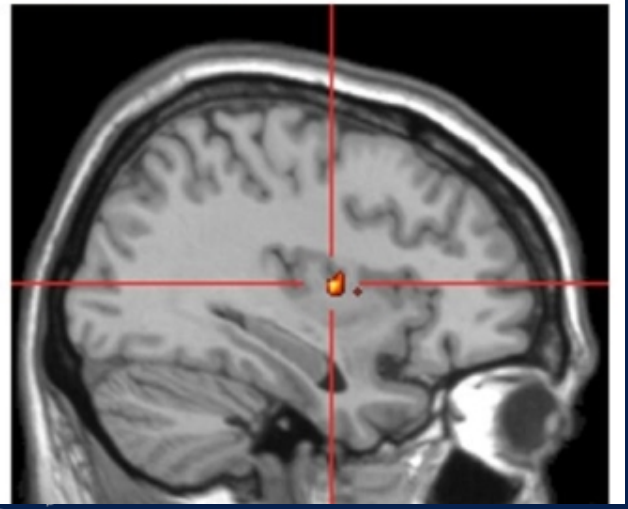
Virtual Reality Buffet

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.

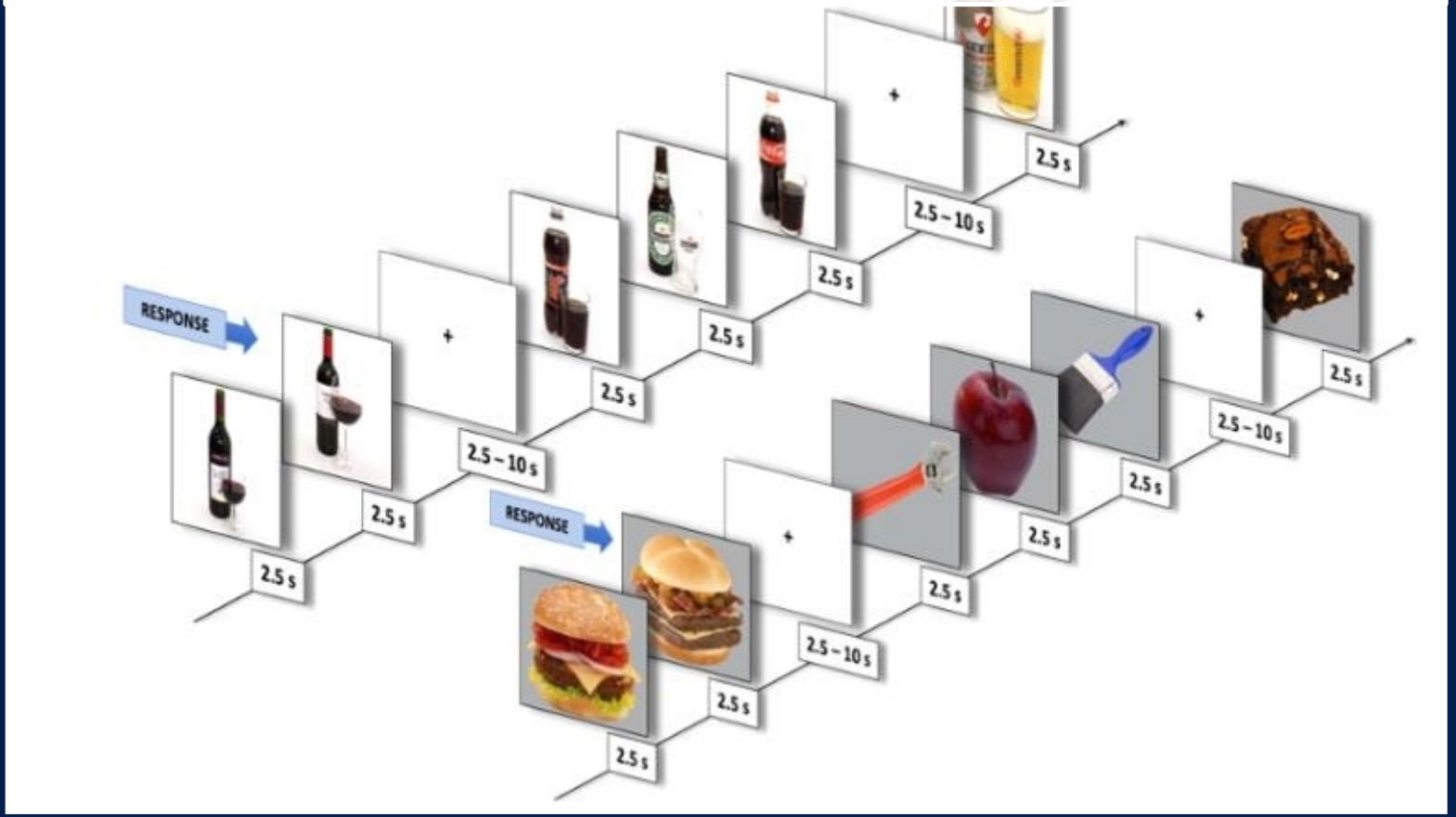
Cue Reactivity in the Mock Bar

Brain Functional MRI





Cue Reactivity Task



Demographics of Enrolled Patients

Characteristic	STAR-B (n=10)	Klausen *et al.* (n=127)
Male Sex	7 (70%)	76 (59.8%)
Age <40	3 (30%)	15 (11.8%)
*Body Mass Index (<30 vs. 30+)	31.0 (25.7-38.5)	26.7
Comorbid Cannabis Use Disorder	4 (40%)	Excluded per protocol
Comorbid Tobacco Use Disorder	4 (40%)	NR but not exclusionary
Comorbid Depression/Anxiety	8 (80%)	NR but not exclusionary
Significant but Stable Medical Comorbidity (but not diabetes)	2 (20%)	NR but not necessarily

Demographics of Enrolled Patients

Characteristic	STAR-B (n=10)	Klausen *et al.* (n=127)
Severe AUD (>5 DSM-5 criteria)	7 (70%)	104 (81.2%)
Mean Drinks Per Day STAR: 28-Day TLFB, 14 g EtOH/drink Danes: 30-Day TLFB, 12 g EtOH/drink	6.16 (US definition) (43.12/week)	4.94 (US definition) 5.76 (Danish definition)
+Mean Heavy Drinking Days Danes: >48g (♀) or 60g (♂) EtOH/day STAR: >42g (♀) or 56g (♂) EtOH/day	16.2	17.0
*High Weekly Alcohol Drinking STAR: >14 (♀) or 21 (♂) drinks/week Danes: >17 heavy drinking days/month	8 (80%)	57 (44.9%)

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

Why the need for caution?

Feb 7
Chloroquine reported to have in-vitro efficacy[7]

Mar 17
French
improve

Mar
WHO
clinic

Jun 5
Study by Mehra
et al formally
retracted[42]

Jun 5
RECOVERY trial ends
hydroxychloroquine study
after finding no benefit[44]

cal trial
cerns

Jun 15
FDA revokes emergency authorisation for use in COVID-19 patients[45]

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation m…ide, are b… widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Althoug… …erall… …e whe… used for approved indications such as autoimmune disease or malaria, the safety and bene… …f th… …treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine … …oquine with… …thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp… …s in s… …ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory t… …g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn… …included in … …of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor… …ne alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed … control gr… . Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or …le they w… …on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc… …of int… …t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (… …tained or… …ed ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) … …OVID-19 were hospitalised during the study period and met the inclusion criteria. Of the… … patie… …were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with … macro… …e, 3016 …eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and a… … pati… …in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple … fou… …ctors (… …sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac… … diabetes… …derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), wh… …mpared wi… …ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95%… …1·22… …457), hydr… …chloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·…18–1·531), … …chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated … …an increased … …f in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6… …; 2·36… …935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; …1, 7… …0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate… …an inc… …ed risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati… …we w… …unabl… …nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macro… …on in… …spital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospita… …reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding William… …ey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

…d Online …22, 2020 …https://doi.org/10.1016/S0140-6736(20)31180-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 29, 2020

See Online/Comment https://doi.org/10.1016/S0140-6736(20)31174-0

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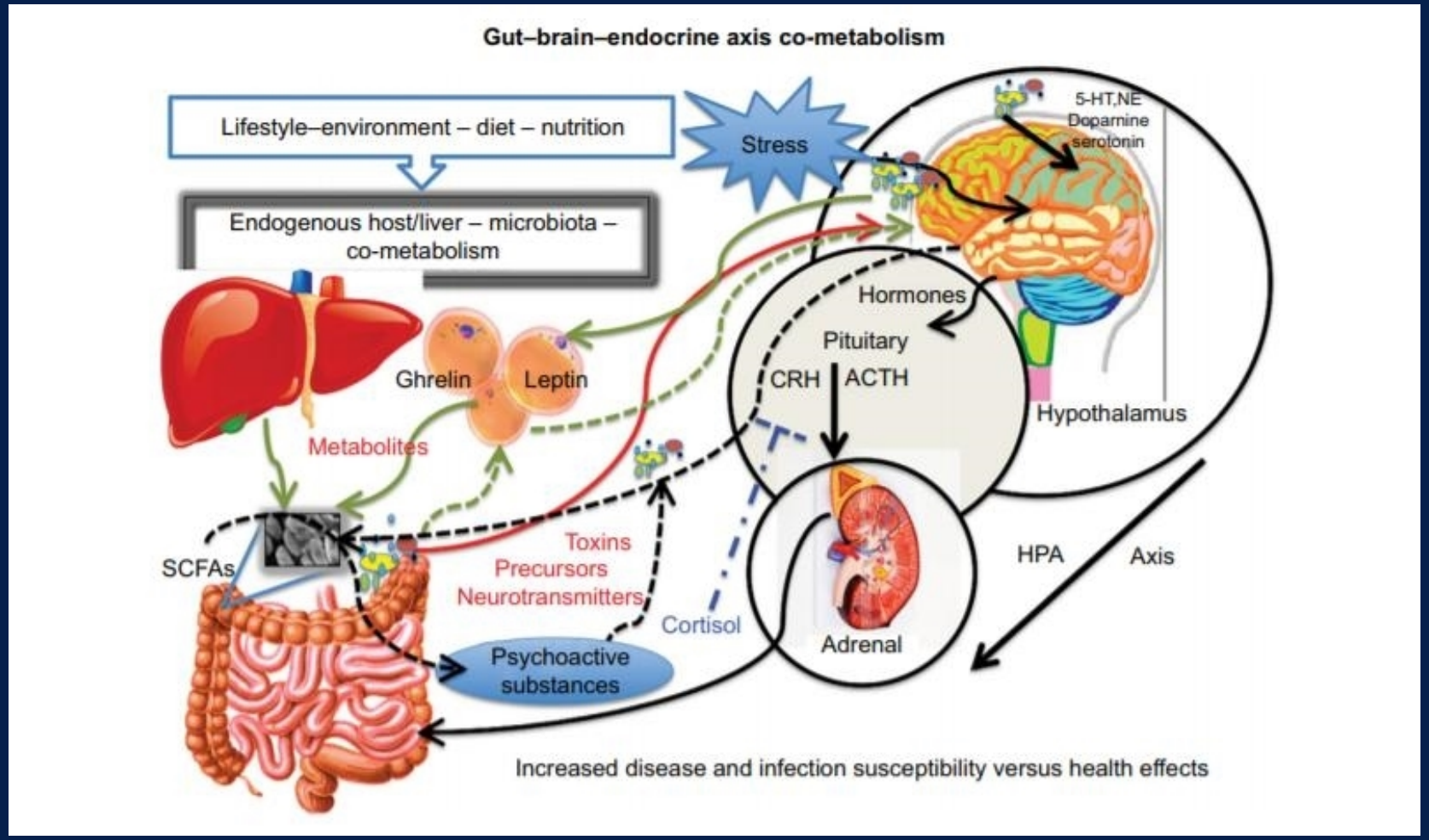
RETRACTED

Stevenson A, *et al*, *Open Heart* 2020;**7:**e001362. doi: 10.1136/openhrt-2020-001362

Mehra, M. R., et al. (2020). *The Lancet*, *395*(10240), 1820.

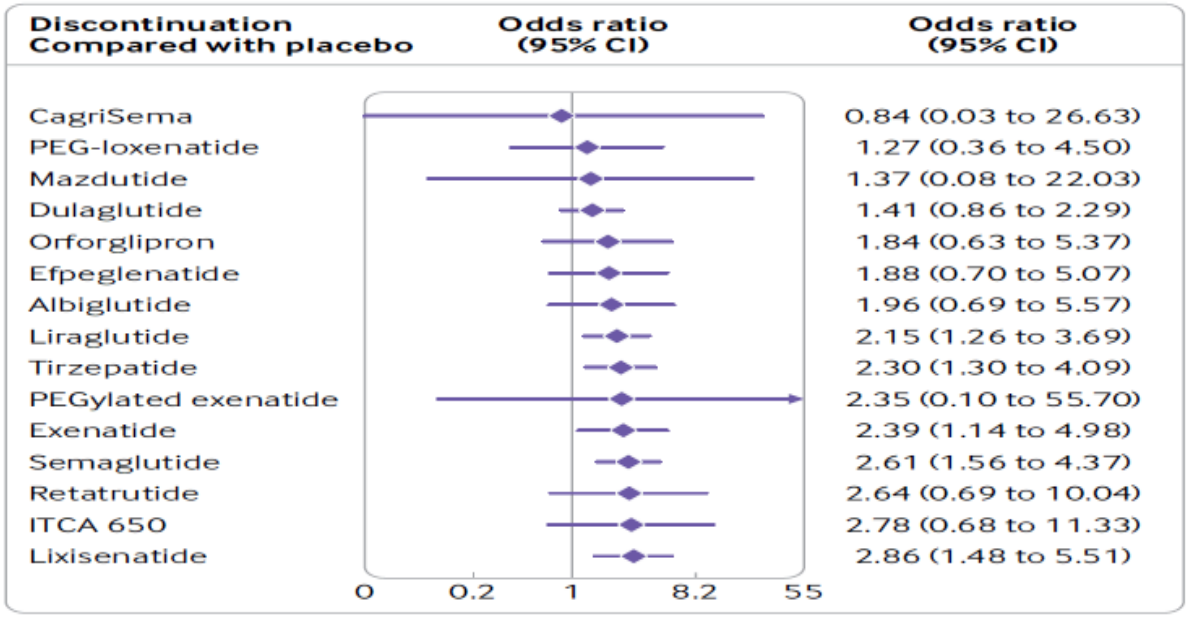
The Brain Does Not Function in Isolation

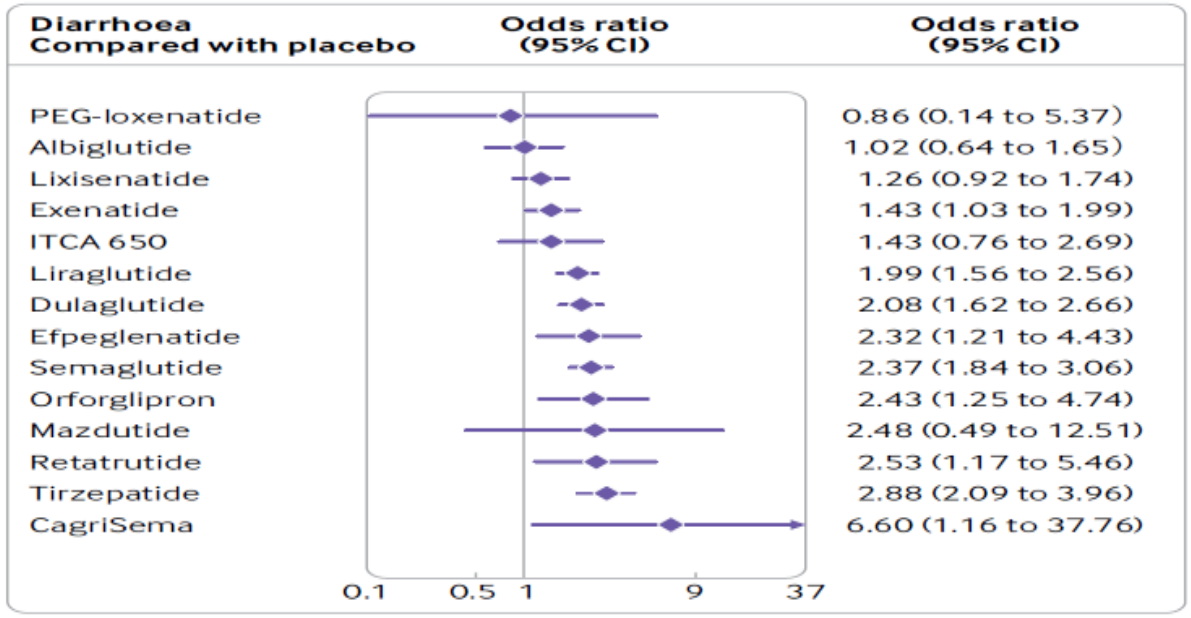


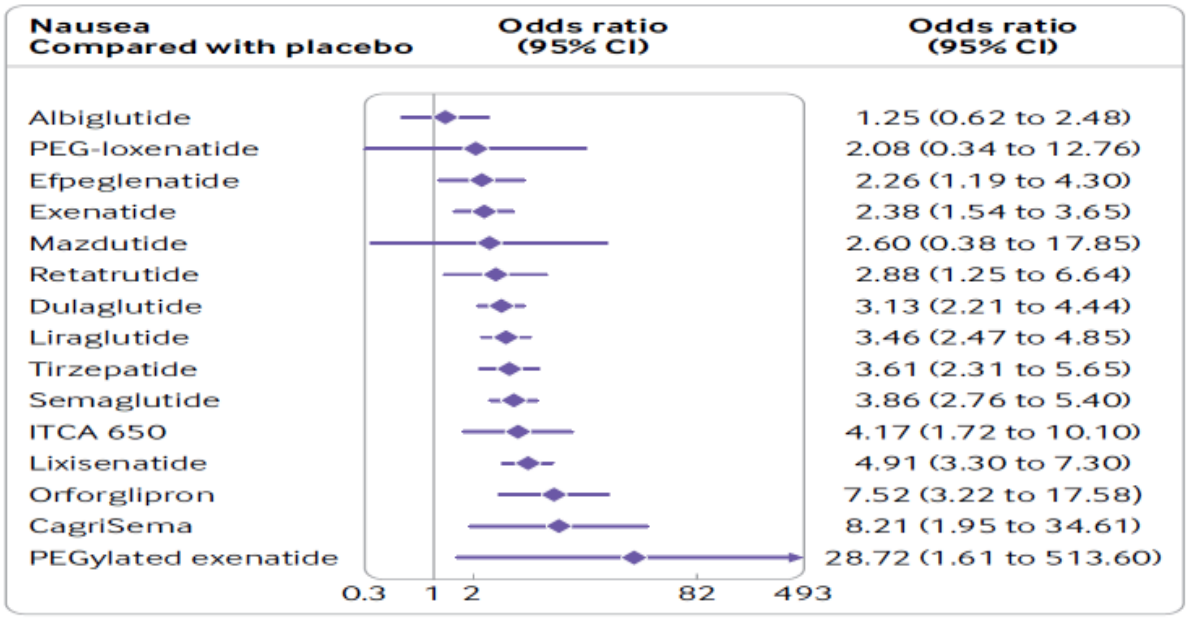
Obrenovich *et al.* Pathology and Laboratory Medicine International (2017) 22 : 21-30.

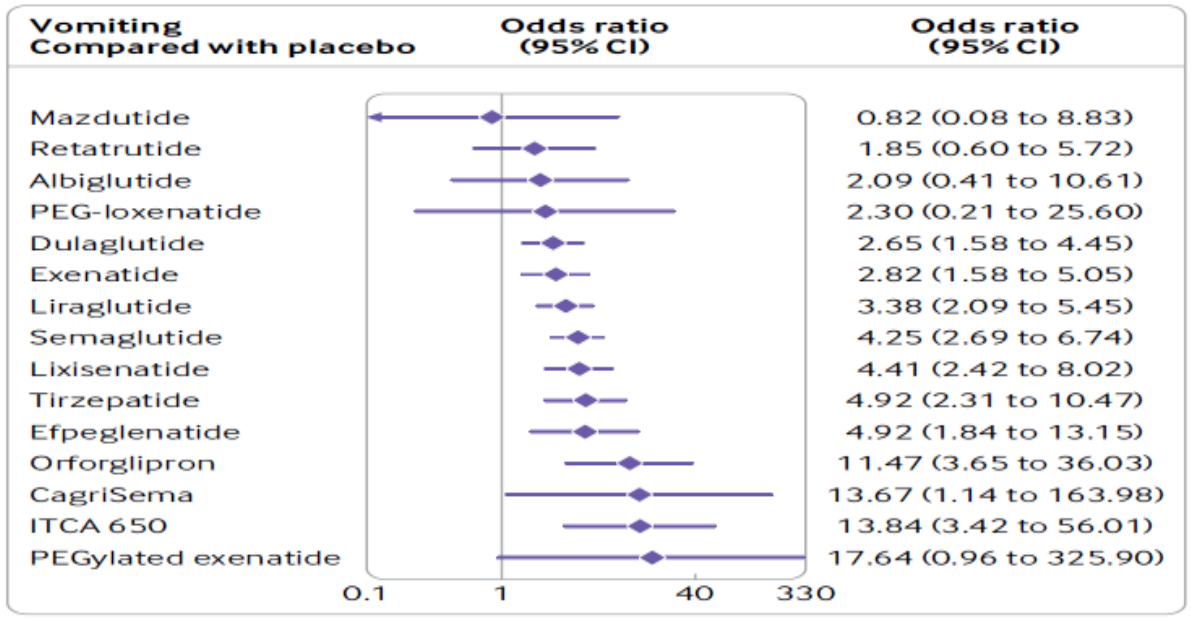
A little reality testing

Jeffrey Brent, M.D., Ph.D.



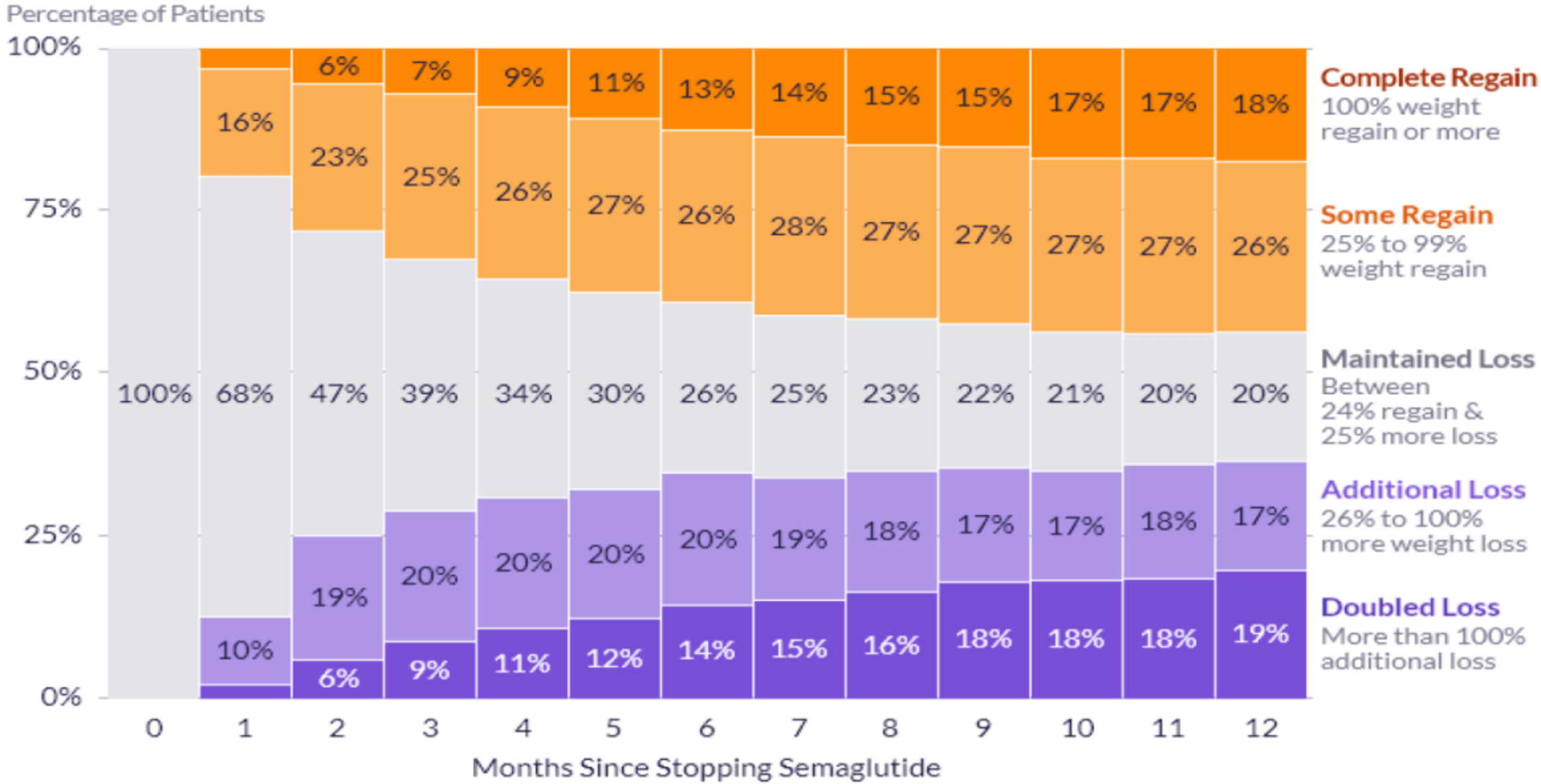






Yao 2024 BMJ 2024;384:e076410

Proportion of Patients by Weight Change After Stopping Semaglutide



N=20,274 patients

"Proportion of Patients by Weight Change After Stopping Semaglutide," 2024. EpicResearch.org

ORIGINAL ARTICLE
Clinical Trials and Investigations

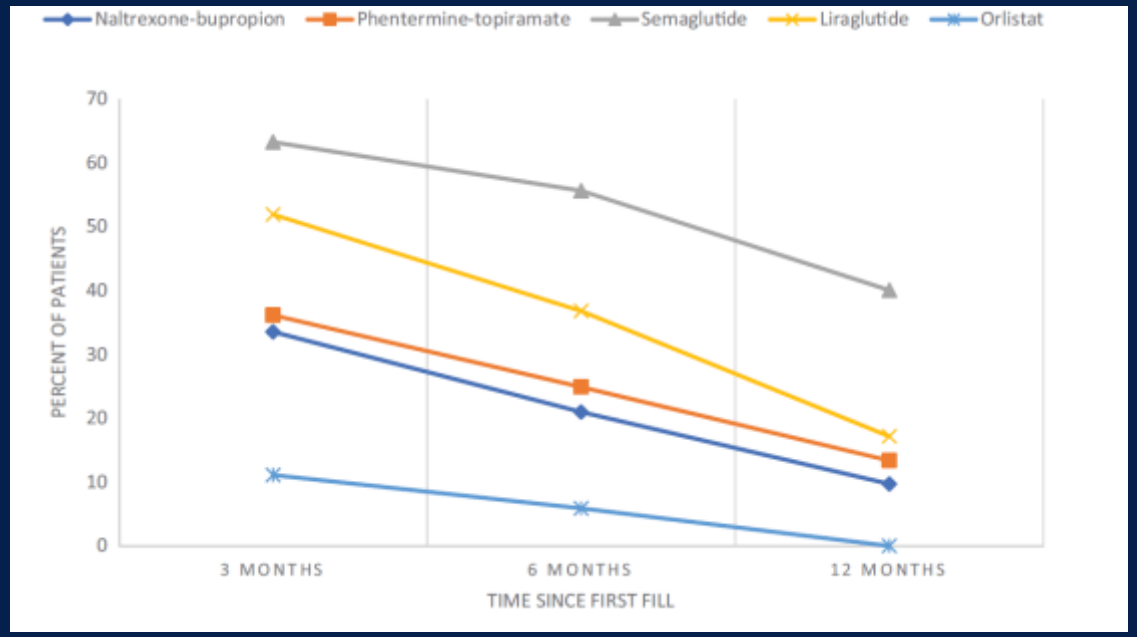
Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Early- and later-stage persistence with antiobesity medications: A retrospective cohort study

Hamlet Gasoyan[1,2] | Elizabeth R. Pfoh[1,2] | Rebecca Schulte[3] | Phuc Le[1,2] | Michael B. Rothberg[1,2]

Patients receiving semaglutide were most likely to not discontinue (40% persistence at 1 year)

Persistence depends on:
- weight loss at 6 months
- Having private insurance



Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension

John P. H. Wilding D.M[1] | Rachel L. Batterham MBBS[2,3,4] |
Melanie Davies M.D[5,6] | Luc F. Van Gaal M.D[7] | Kristian Kandler M.D[8] |
Katerina Konakli PhD[8] | Ildiko Lingvay M.D[9] | Barbara M. McGowan M.D[10] |
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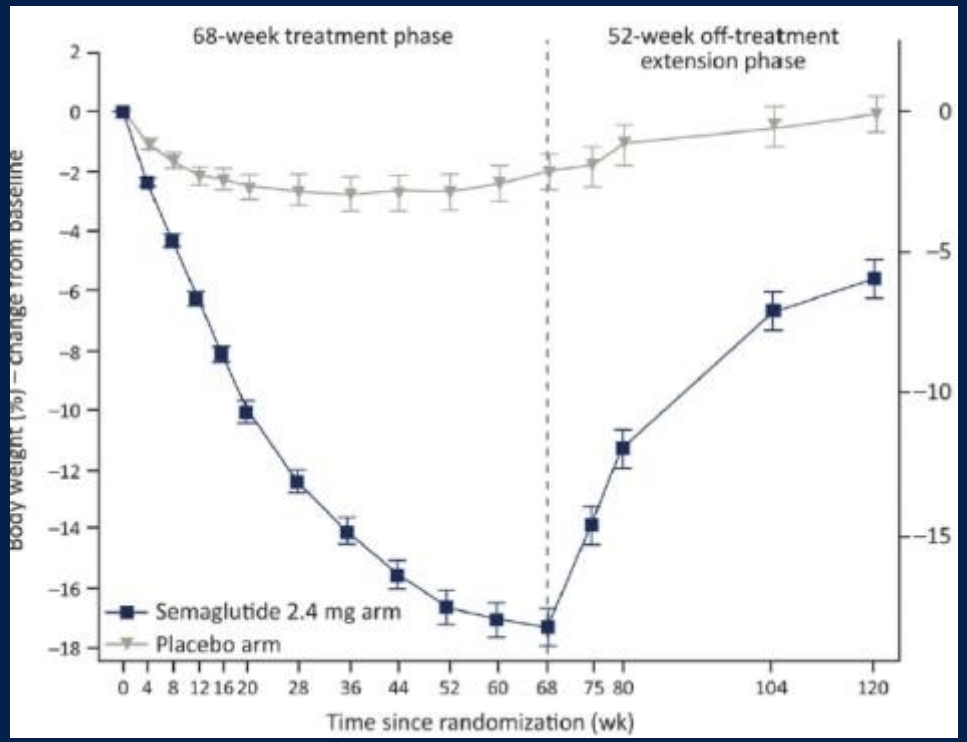
Thomas A. Wadden Ph.D[12] | Sean Wharton M.D[13] | Koutaro Yokote M.D[14] |
Robert F. Kushner M.D[15] | STEP 1 Study Group



Cardiometabolic improvements reversed with weight gain

Diabetes Obes Metab 2022

Despite costs, GLP-1 agonists are in short supply

People are turning to non-traditional sources

Legitimate compounding pharmacies vs. other internet-based sellers

FDA allows compounding pharmacies to distribute drugs in short supply, even if not the actual pharmaceutical preparation

Online pharmacies/compounders may be selling different forms of the drug, such as semaglutide salts or preparations that do not meet USP standards

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- **Access:** Gain access to knowledgeable telehealth care from around the country, not just your local area.*

GLP-1 Agonists do not selectively decrease adipose tissue mass

- Loss of lean body mass assoc w/ loss of strength, quality of life, and increased mortality
- Approximately 35% of wt loss w/ semaglutide is LBM
- Can use hand grip strength to measure muscle mass

“Ozempic Face”

National Broadcasting Company

Maintaining muscle mass during GLP-1 treatment

- Protein intake
  - ≥1.5 g/kg/d
- Strength training
  - At least twice a week

Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

Outcomes	GLP-1 agonists, HR (95% CI)[a]		Bupropion-naltrexone
	Crude	Adjusted[b]	
Primary analysis			
Biliary disease	1.48 (0.88-2.47)	1.50 (0.89-2.53)	1 [Reference]
Pancreatitis	10.33 (1.44-74.40)	9.09 (1.25-66.00)	1 [Reference]
Bowel obstruction	5.16 (1.27-21.00)	4.22 (1.02-17.40)	1 [Reference]
Gastroparesis	3.31 (1.04-10.50)	3.67 (1.15-11.90)	1 [Reference]

Absolute risks
< 1%/yr of use

No increased risk of biliary tract disease

Sodhi et al., JAMA 2023

June 29, 2023

American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Girish P. Joshi, M.B.B.S., M.D., Basem B. Abdelmalak, M.D., Wade A. Weigel, M.D., Sulpicio G. Soriano, M.D., Monica W. Harbell, M.D., Catherine I. Kuo, M.D., Paul A. Stricker, M.D., Karen B. Domino, M.D., M.P.H., American Society of Anesthesiologists (ASA) Task Force on Preoperative Fasting

GLP-1RAs decrease gastric emptying

Day(s) Prior to the Procedure:

- For patients on daily dosing consider holding GLP-1 agonists on the day of the procedure/surgery. For patients on weekly dosing consider holding GLP-1 agonists a week prior to the procedure/surgery.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02672-2

Association of semaglutide with risk of suicidal ideation in a real-world cohort

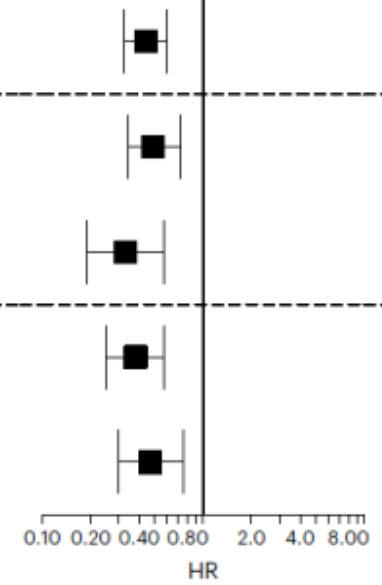
Received: 31 July 2023

Accepted: 30 October 2023

William Wang[1], Nora D. Volkow[2] ✉, Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] & Rong Xu[5] ✉

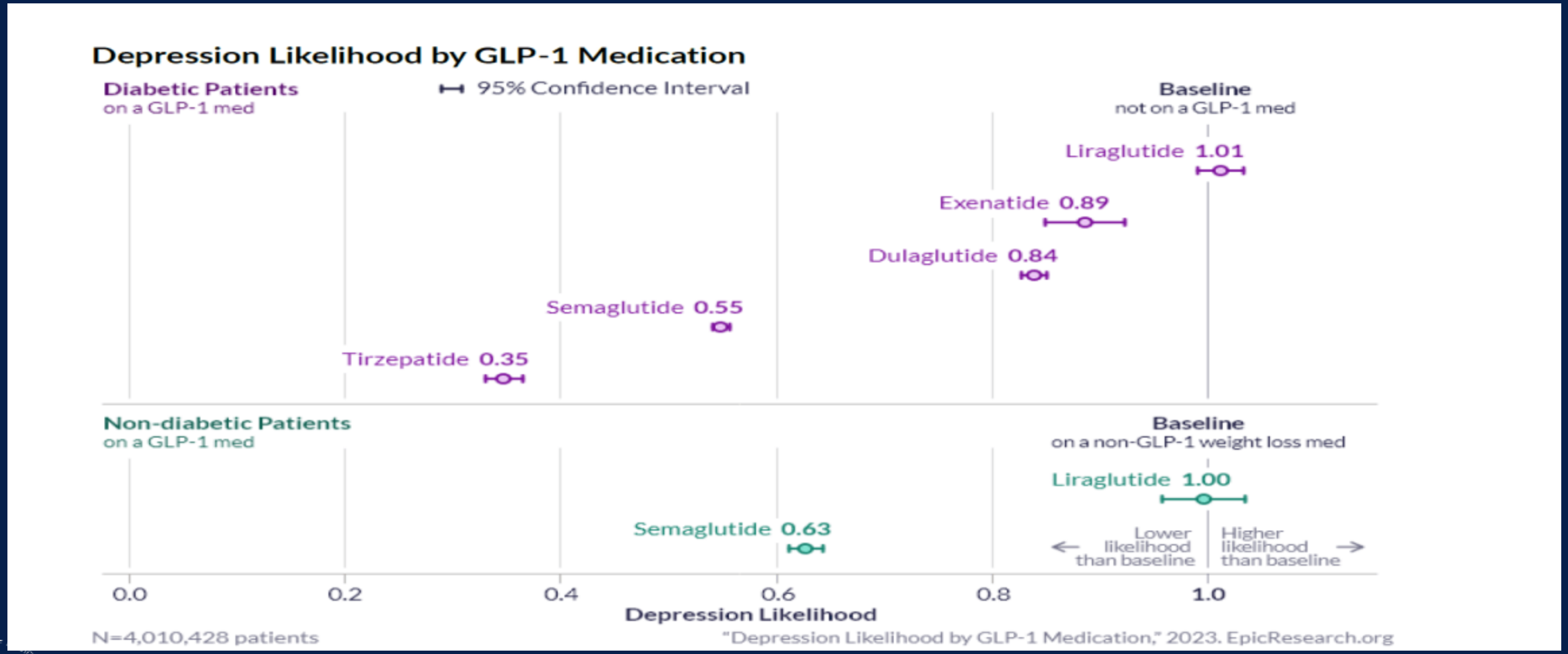
a

Population	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	HR (95% CI)
Overall (*n* = 865 per group)	6.5% (56)	14.1% (122)	0.44 (0.32–0.60)
Females (*n* = 618 per group)	6.5% (40)	12.8% (79)	0.49 (0.34–0.72)
Males (*n* = 234 per group)	7.3% (17)	20.1% (47)	0.33 (0.19–0.57)
Age ≤45 years (*n* = 446 per group)	6.7% (30)	17.3% (77)	0.38 (0.25–0.57)
Age >45 years (*n* = 409 per group)	6.4% (26)	12.7% (52)	0.47 (0.30–0.76)

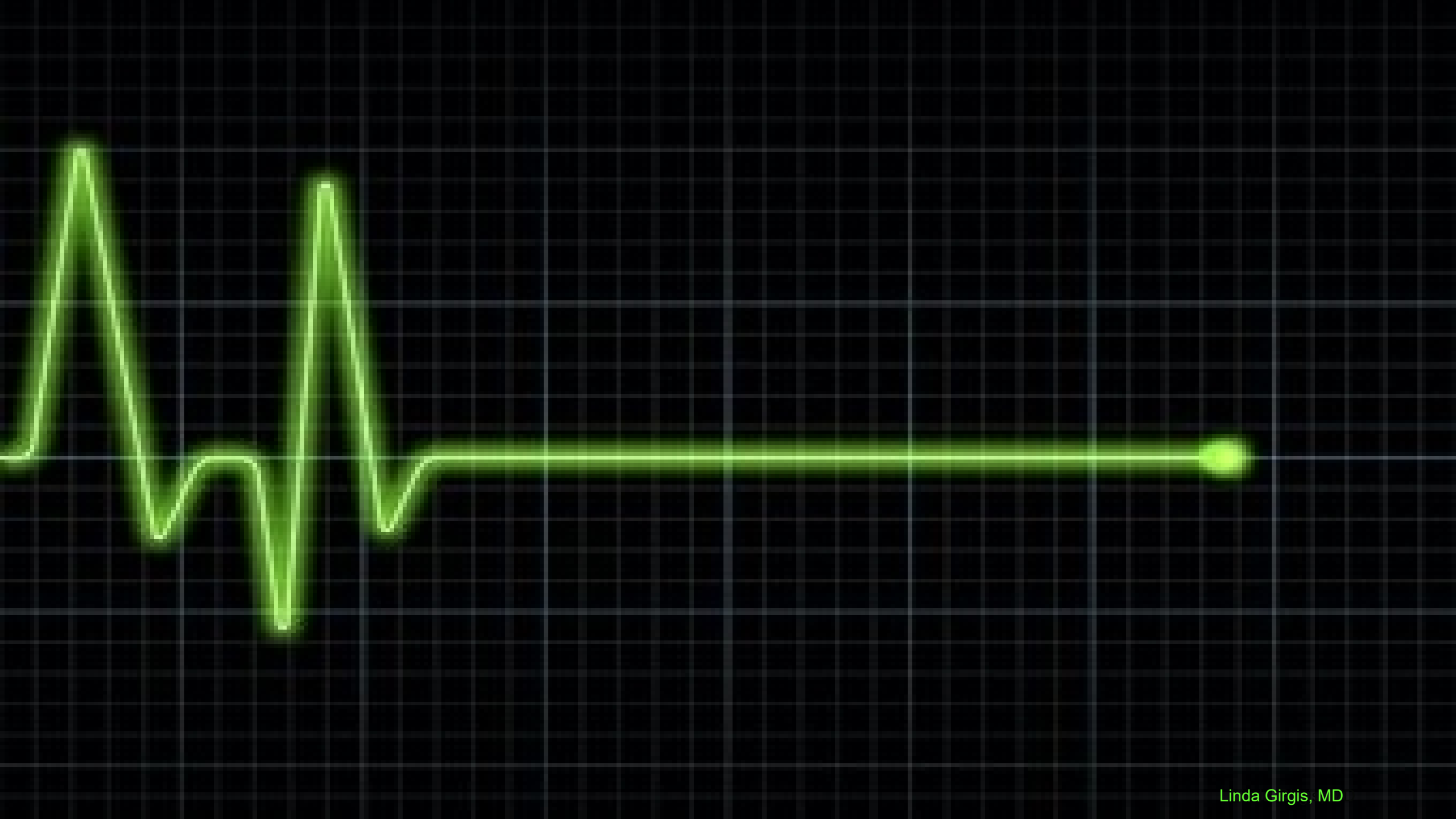


Nature Medicine, 2024

GLP-1RAs Have an Antidepressant Effect



EPIC Research

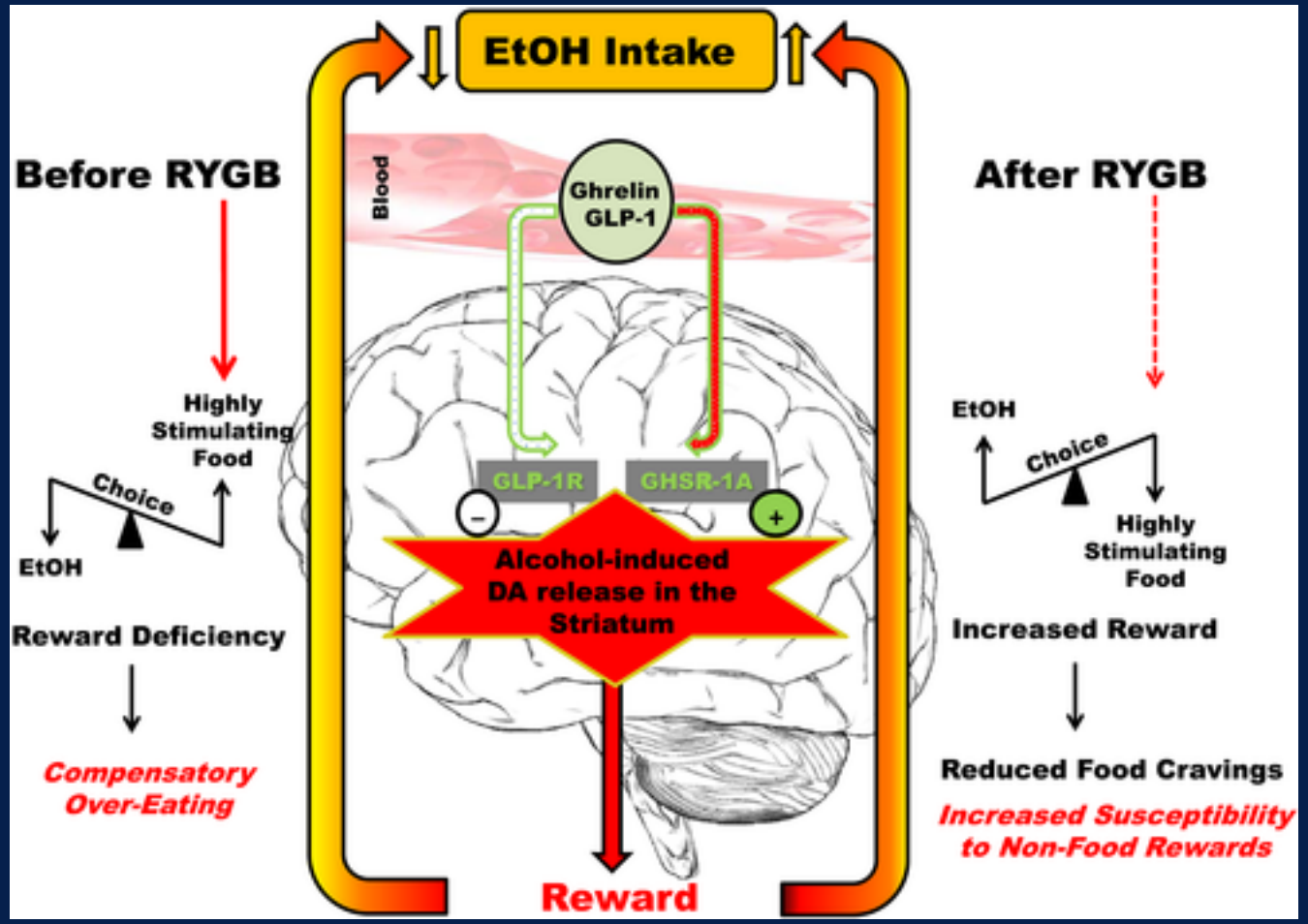


Linda Girgis, MD

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.

Bariatric Surgery and AUD



Blackburn, A.N, *et al.* (2016) *Addiction Biology*, *22*(6): 1540-1553