



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

Overview of GLP-1 Receptor Agonists



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The background features a dark blue field with a vertical strip on the left containing a complex network of white lines and dots. Various medical and scientific icons are scattered throughout, including a caduceus, a brain, a heart, and a DNA helix. The words "HEALTHCARE" and "SCIENCE" are also visible in a stylized font.

Disclosure Information

Joji Suzuki, MD

- *Indivior: Other Research Support
(includes receipt of drugs, supplies,
equipment or other in-kind support)
(Terminated, August 1, 2023)*

**2023 BREAKTHROUGH
OF THE YEAR**



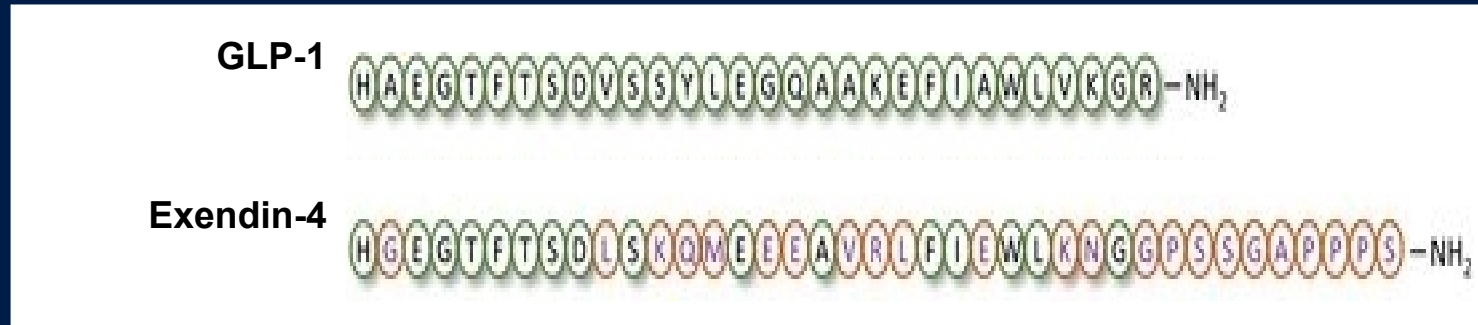
GLP-1 THERAPIES
Science

Discovery of GLP-1 Receptor Agonist

Discovered in 1991, exendin-4—a 39-amino acid peptide found in the venom of the Gila Monster—is a hormone that is structurally similar to a human hormone that was already being researched called glucagon-like peptide-1 (GLP-1).

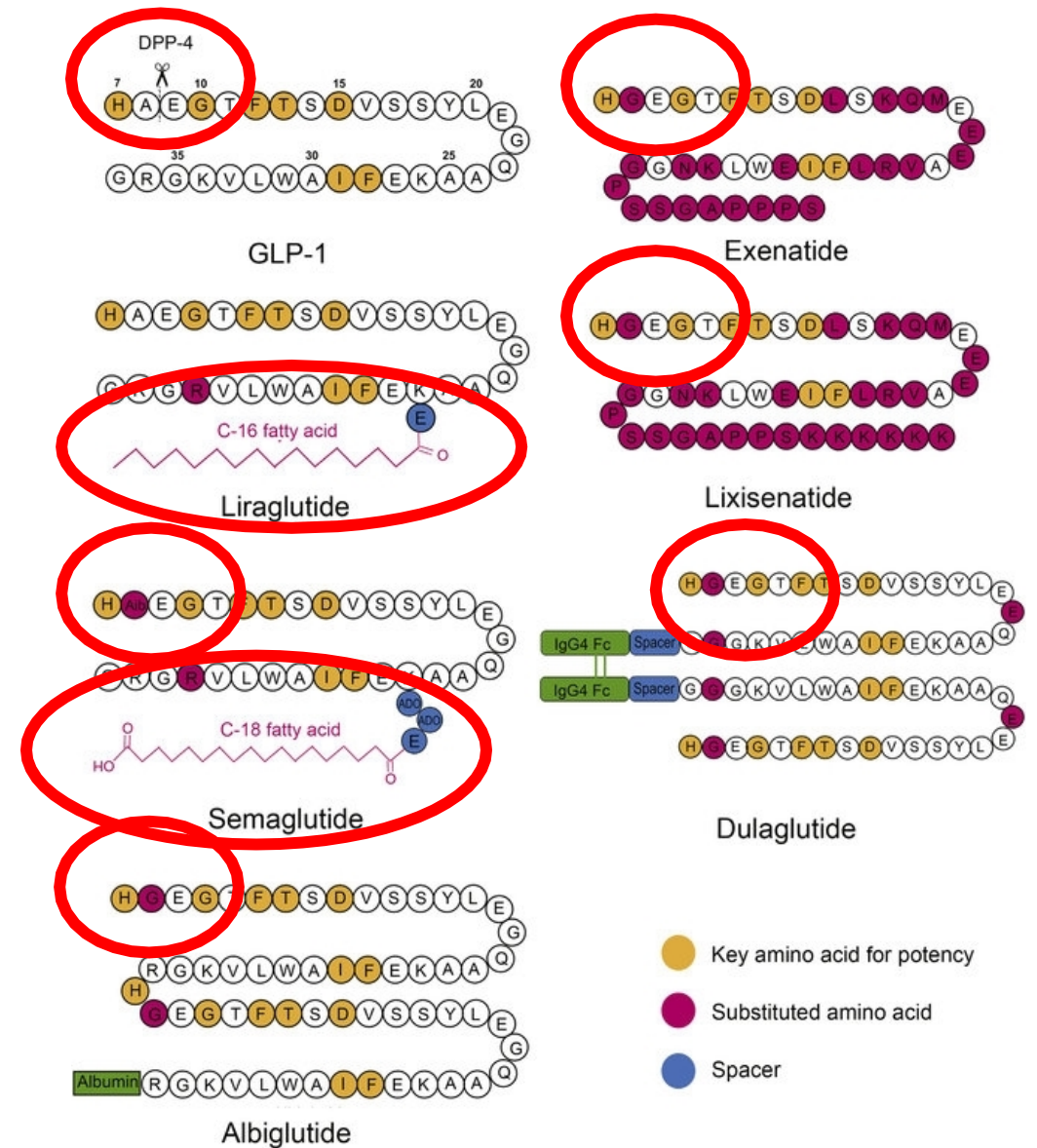


Discovery of GLP-1 Receptor Agonist

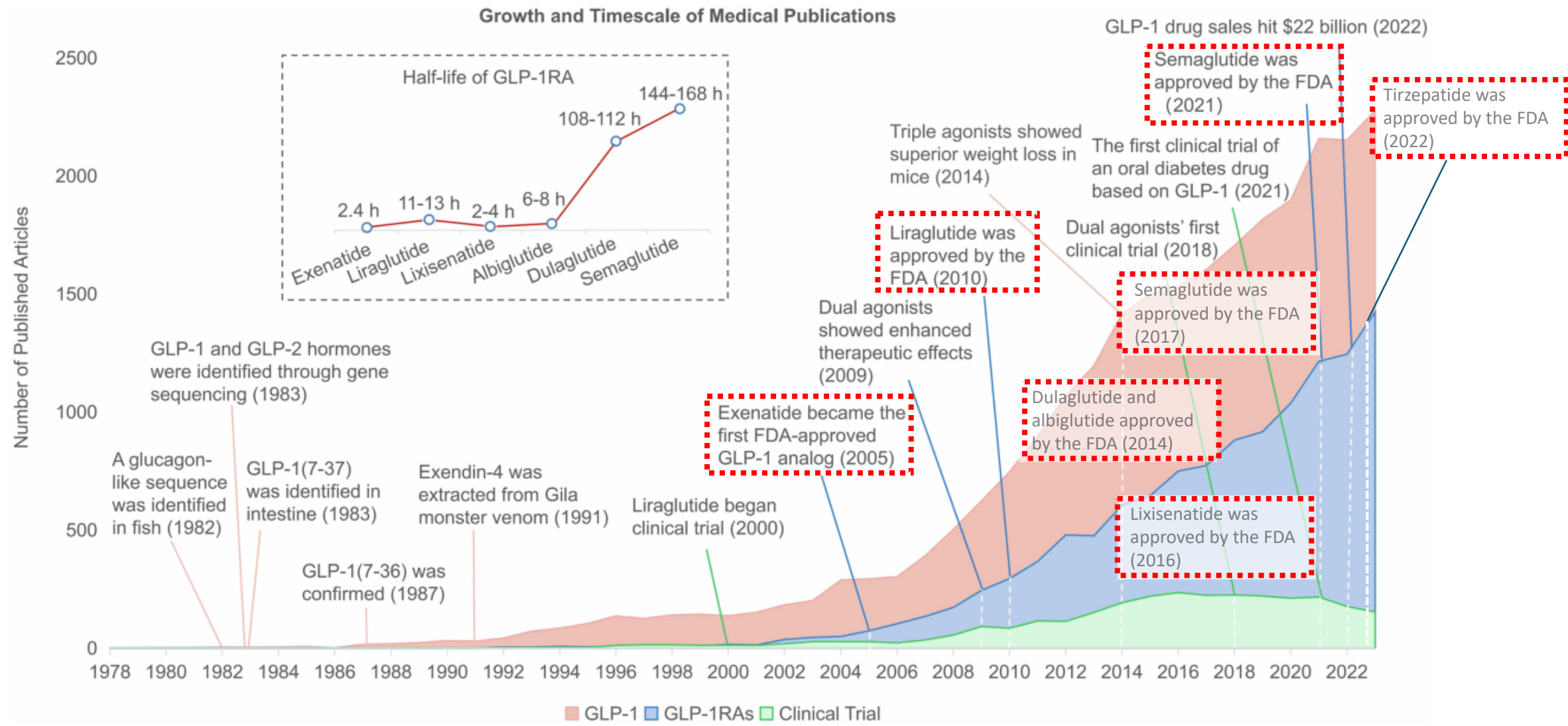


- GLP-1s were known to increase the release of insulin but had an extremely short half-life (1-2 minutes), making it unsuitable as a treatment for diabetes.
- Exendin-4 had a half-life about 2.4 hours, almost 100 times longer!

Subsequent research focused on increasing half-life, resist degradation, and enhance binding to the GLP-1 receptor.



Growth and Timescale of Publications on GLP-1RAs



Single-agonist medications

Glucagon-Like
Peptide-1
(GLP1)
agonists

Glucose-
dependent
Insulinotropic
Polypeptide
(GIP) agonists

Glucagon
agonists

Dual-agonist medication (tirzepatide)

Triple-agonist medication (retatrutide)



Food Intake



Intestines

Brain



↑ Satiety
↓ Food intake

GLP-1

Pancreas



↑ insulin
↓ glucagon

Stomach



↓ gastric emptying
↓ gastric motility

Liver



↓ Liver fat
↓ Glucose production

Food Intake



Intestines

Brain



↓ Food intake

GIP

Pancreas



↑ insulin
↑ glucagon

Stomach

↓ gastric emptying
↓ gastric motility

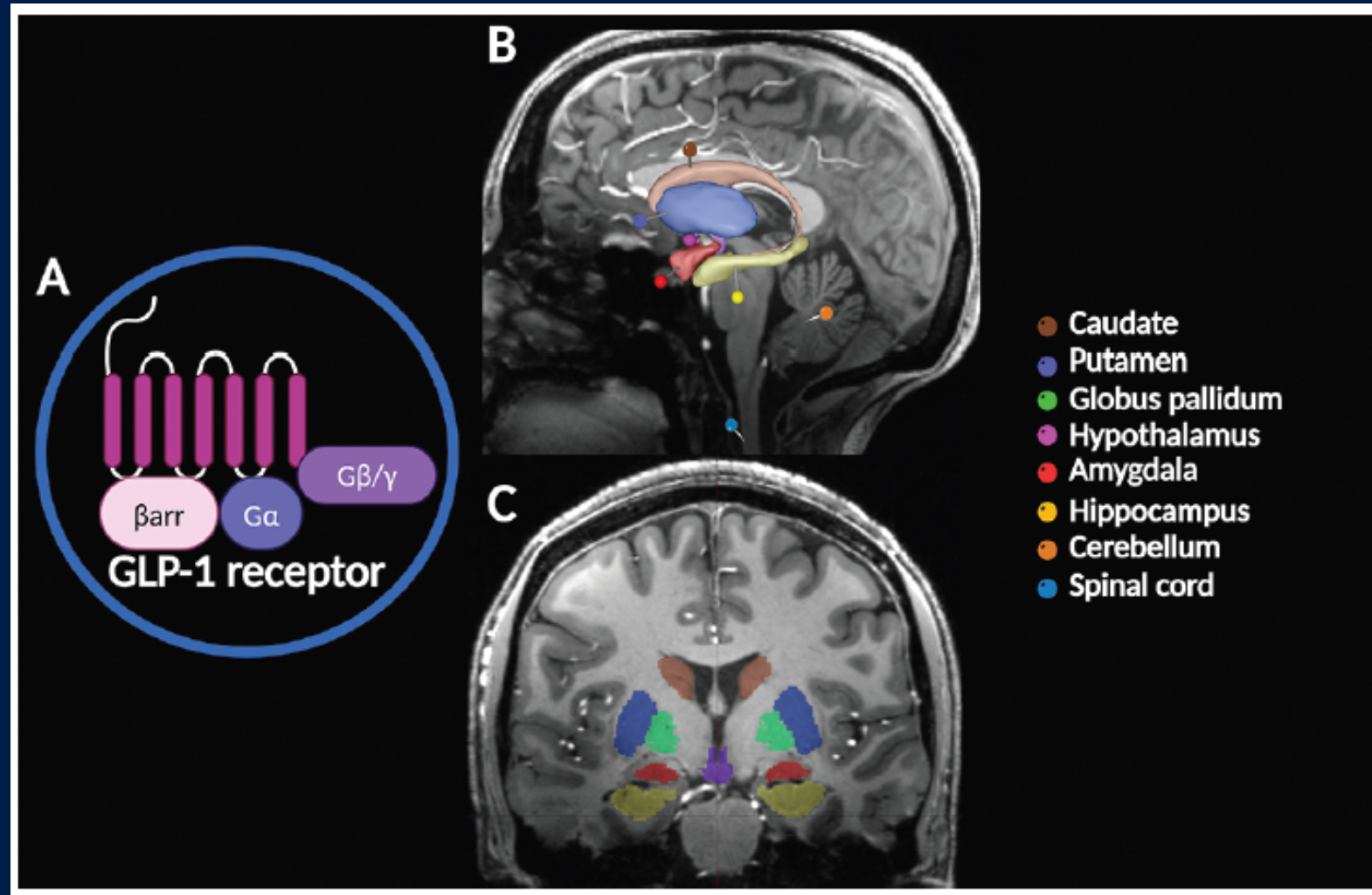


Liver

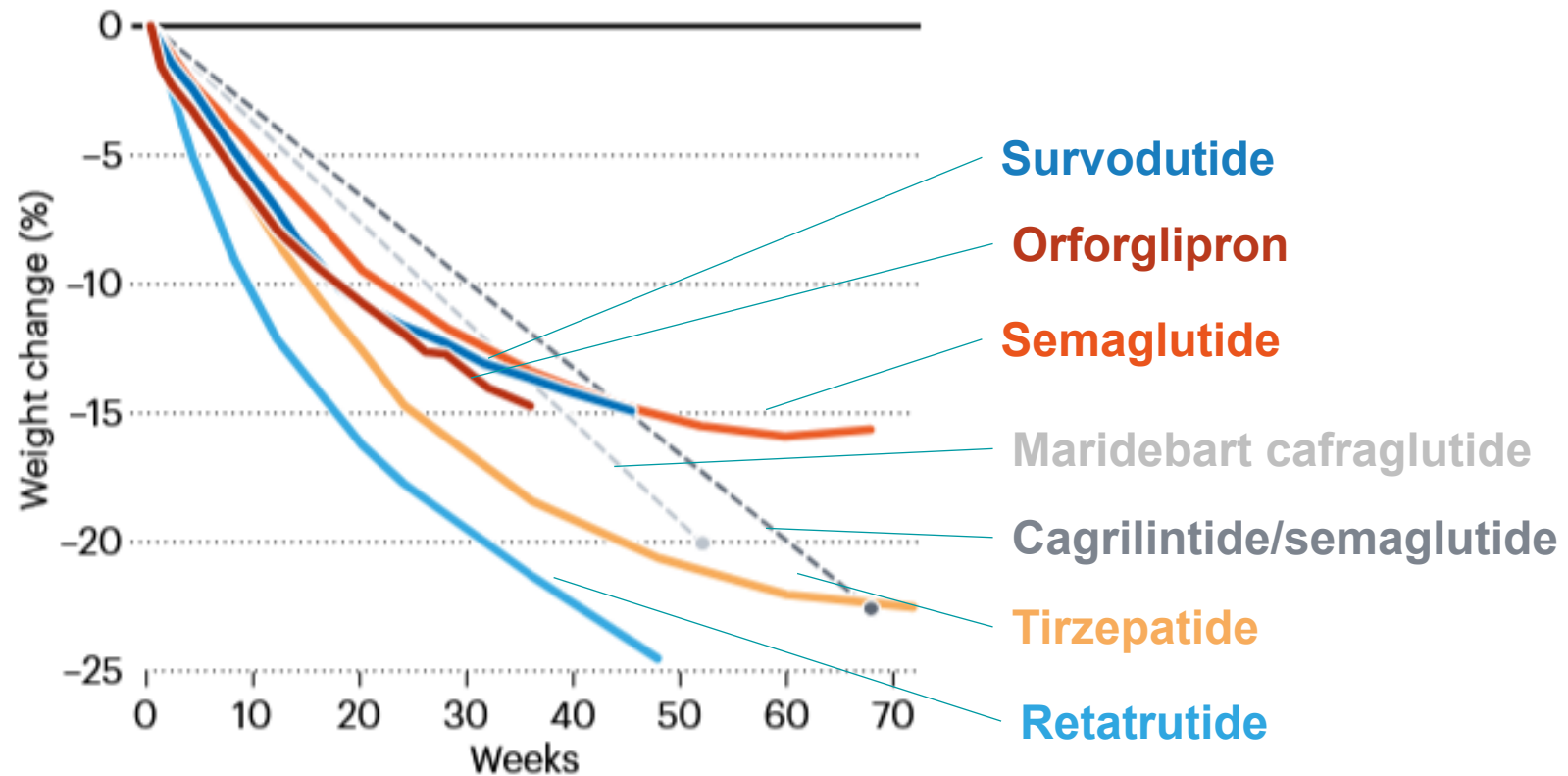


↑ Liver fat

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



Next-generation obesity drugs are arriving soon



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

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

Research

JAMA Psychiatry | Brief Report

Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder

Markku Lähteenvuo, MD, PhD; Jari Tiihonen, MD, PhD; Anssi Solismaa, MD, PhD; Antti Tanskanen, PhD; Ellenor Mittendorfer-Rutz, PhD; Heidi Taipale, PhD

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:

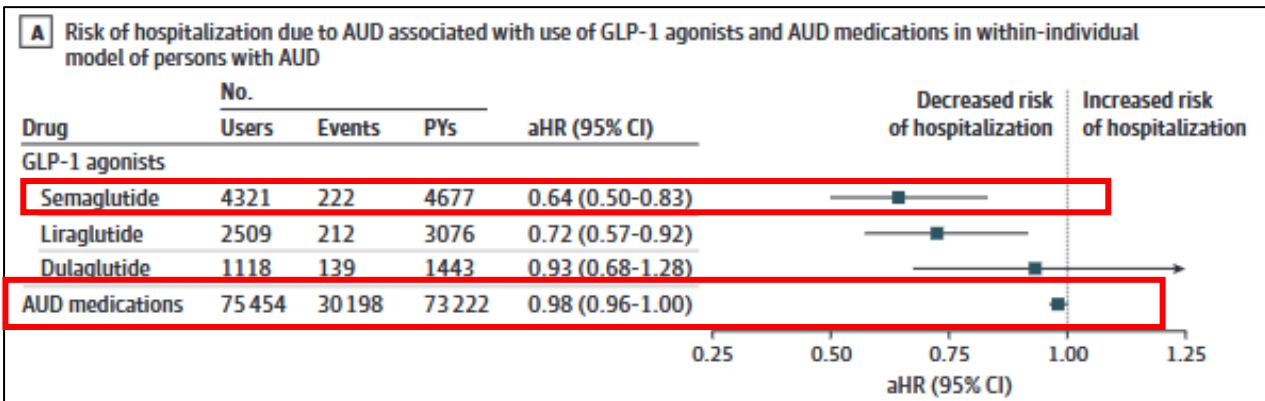
- Use of GLP-1 vs non-use of GLP-1
- Use of MAUD medications

Outcomes:

- AUD-related hospitalization
- Any SUD-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

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

nature communications



Article

<https://doi.org/10.1038/s41467-024-48780-6>

Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population

Received: 8 November 2023

Accepted: 8 May 2024

William Wang¹, Nora D. Volkow²✉, Nathan A. Berger³, Pamela B. Davis³,
David C. Kaelber⁴ & Rong Xu⁵✉

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
- Assess for incident and recurrent AUD, assessed separately by age, sex, and race

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.
- 83,325 patients with obesity without prior AUD
 - Incident AUD: **HR: 0.50**
- 4,254 patients with obesity with prior AUD
 - Recurrent AUD: **HR: 0.44**
- 598,803 patients with T2D without AUD
 - Incident AUD: **HR: 0.56**
- 22,113 patients with T2D with prior AUD
 - Recurrent AUD: **HR: 0.61**

Conclusions: Results point to a potential benefit of semaglutide for AUD

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

JAMA
Network | Open.

Research Letter | Psychiatry

Semaglutide and Opioid Overdose Risk in Patients With Type 2 Diabetes and Opioid Use Disorder

William Wang, Nora D. Volkow, MD; QuangQiu Wang, MS; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; Rong Xu, PhD

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)

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 .

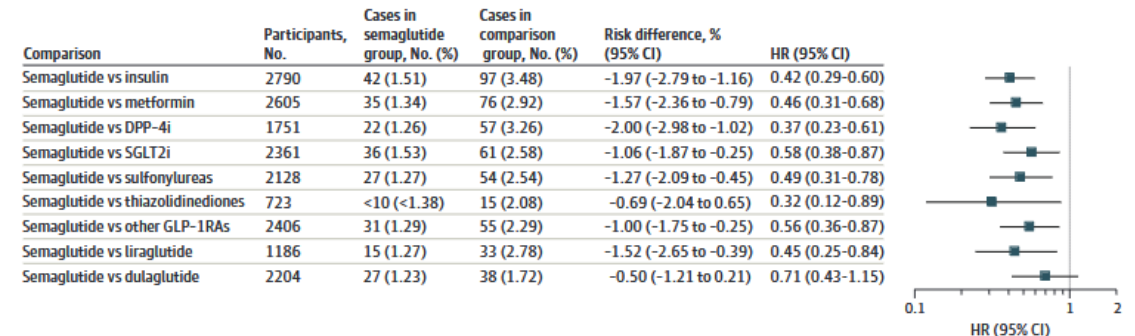
Exposure:

- Semaglutide vs other antidiabetic medications between 2017 and 2023.

Outcomes:

- Opioid overdose

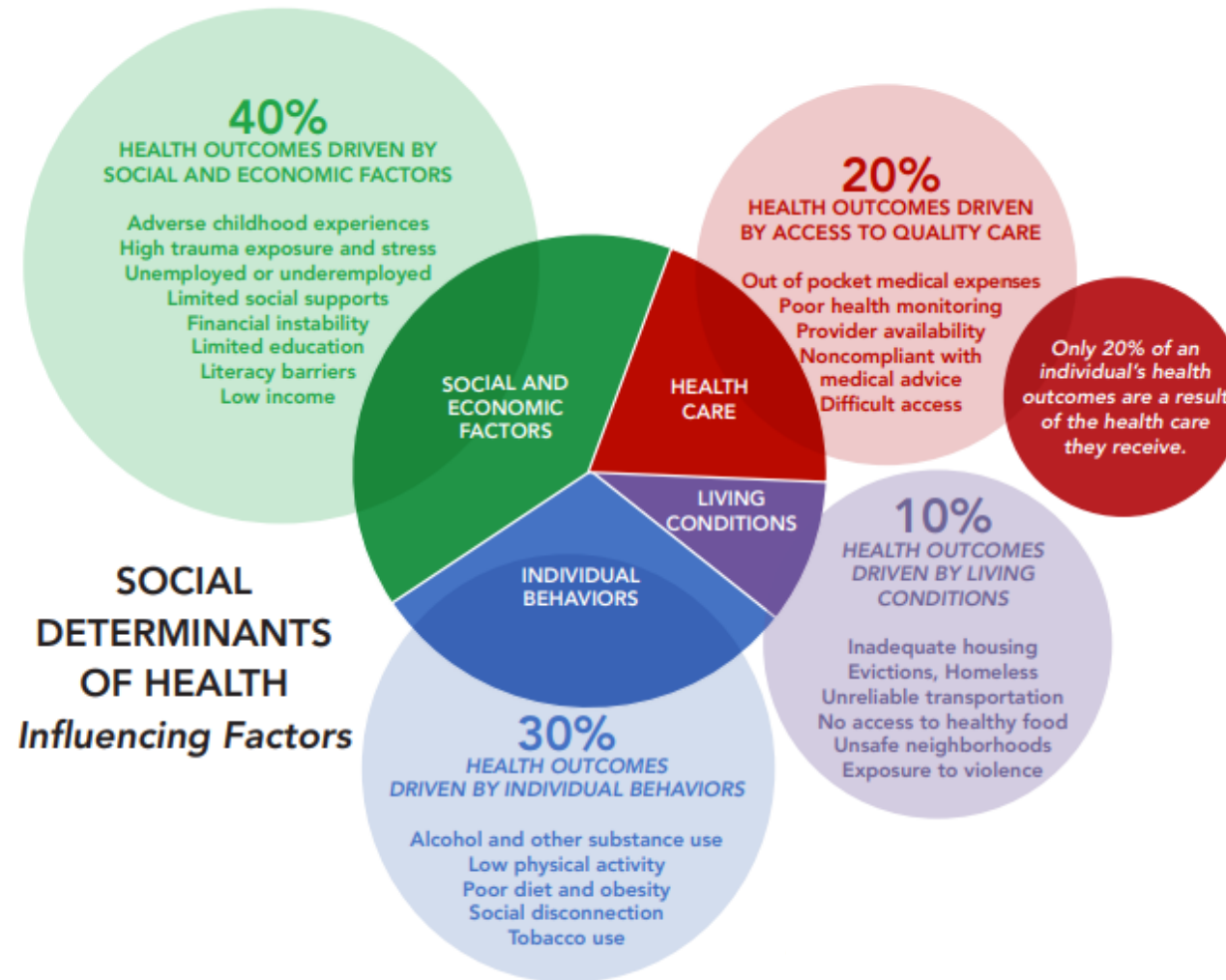
Figure. Risk of Opioid Overdose in Patients With Type 2 Diabetes and Opioid Use Disorders, Comparing Propensity-Score Matched Semaglutide With Other Antidiabetic Medication Groups



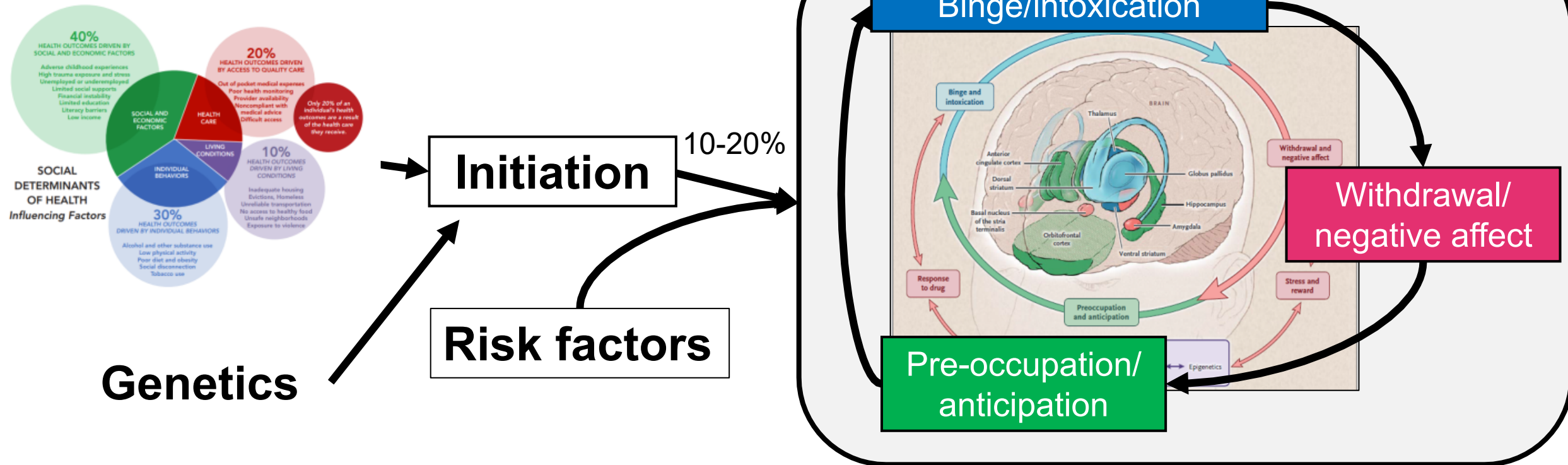
Conclusions:

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

Development of substance use disorders



Development of substance use disorders



Theoretical models of substance use disorders



Disrupted self-processing

- Maladaptive self-referential thoughts
- Default mode network

Self-referential
rumination



Operant Conditioning

- "Liking"
- Reward network

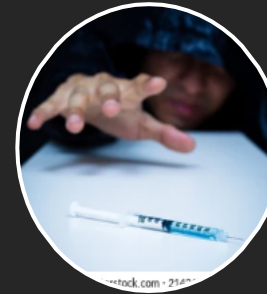
Binge/
intoxication



Opponent-process

- Reward vs anti-reward
- HPA

Withdrawal/
Negative affect



Incentive sensitization

- "Craving"
- Salience network

Pre-occupation/
Anticipation



Impaired regulation

- Poor inhibitory control
- Executive network

Loss of control

Opioid cravings and stress are elevated prior to relapse while taking MOUD

Before and After: Craving, Mood, and Background Stress in the Hours Surrounding Drug Use and Stressful Events in Patients with Opioid-Use Disorder

Kenzie L. Preston^{*,1}, William J. Kowalczyk¹, Karran A. Phillips¹, Michelle L. Jobes¹, Massoud Vahabzadeh², Jia-Ling Lin², Mustapha Mezghanni², and David H. Epstein¹

¹Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD

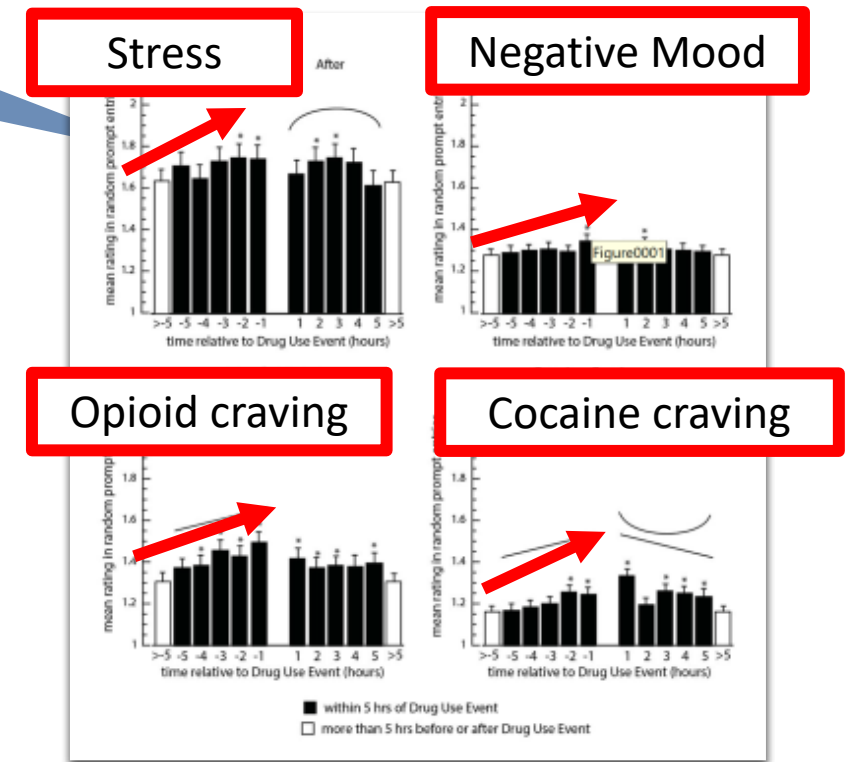
Setting: Outpatient treatment center in Baltimore

Participants: OUD patients on MOUD (n=192)

Design: 16-week prospective study

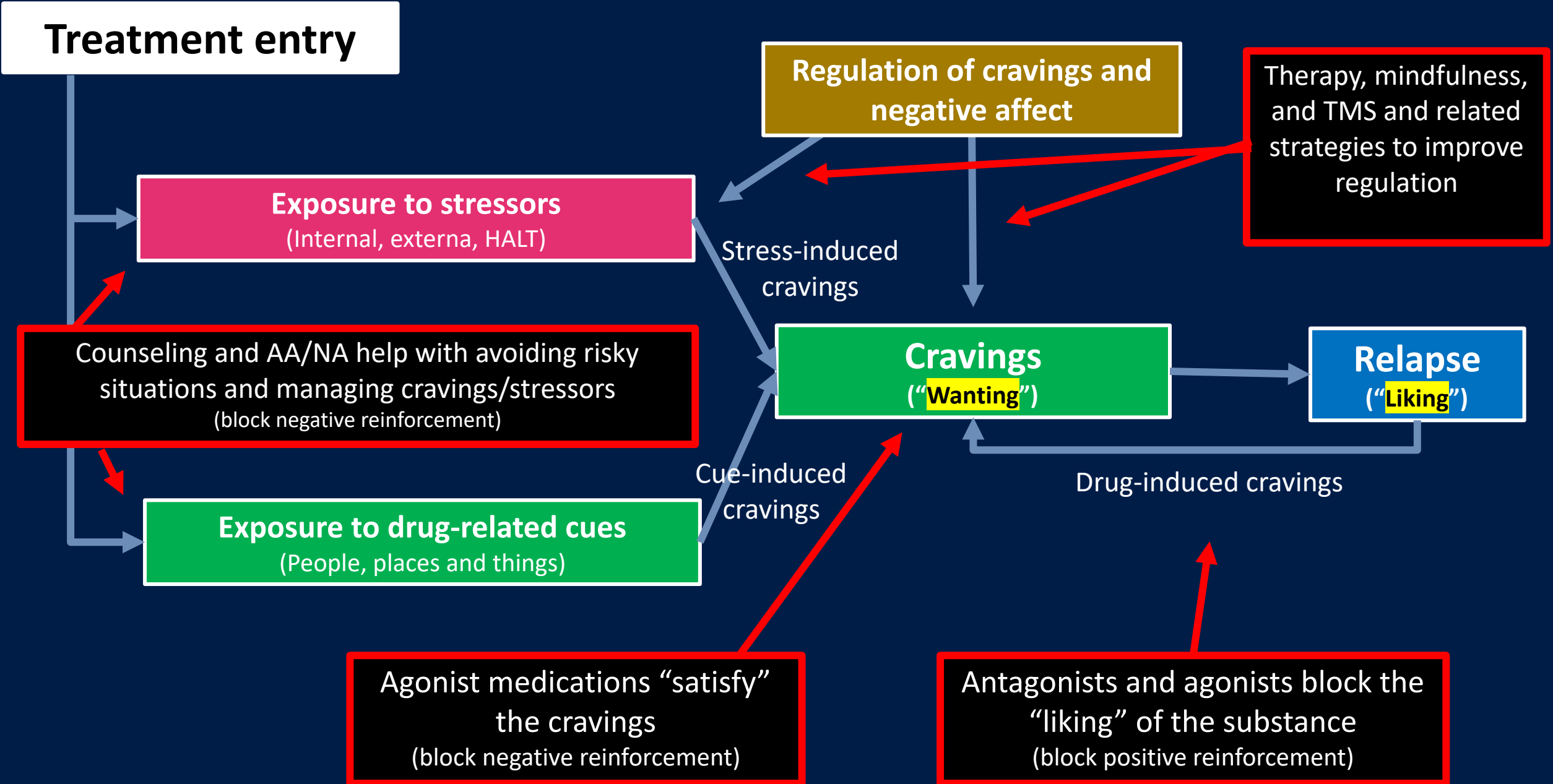
Primary outcome: Smartphone EMA report on cravings, stress, and negative mood within 5 hours before and after use

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

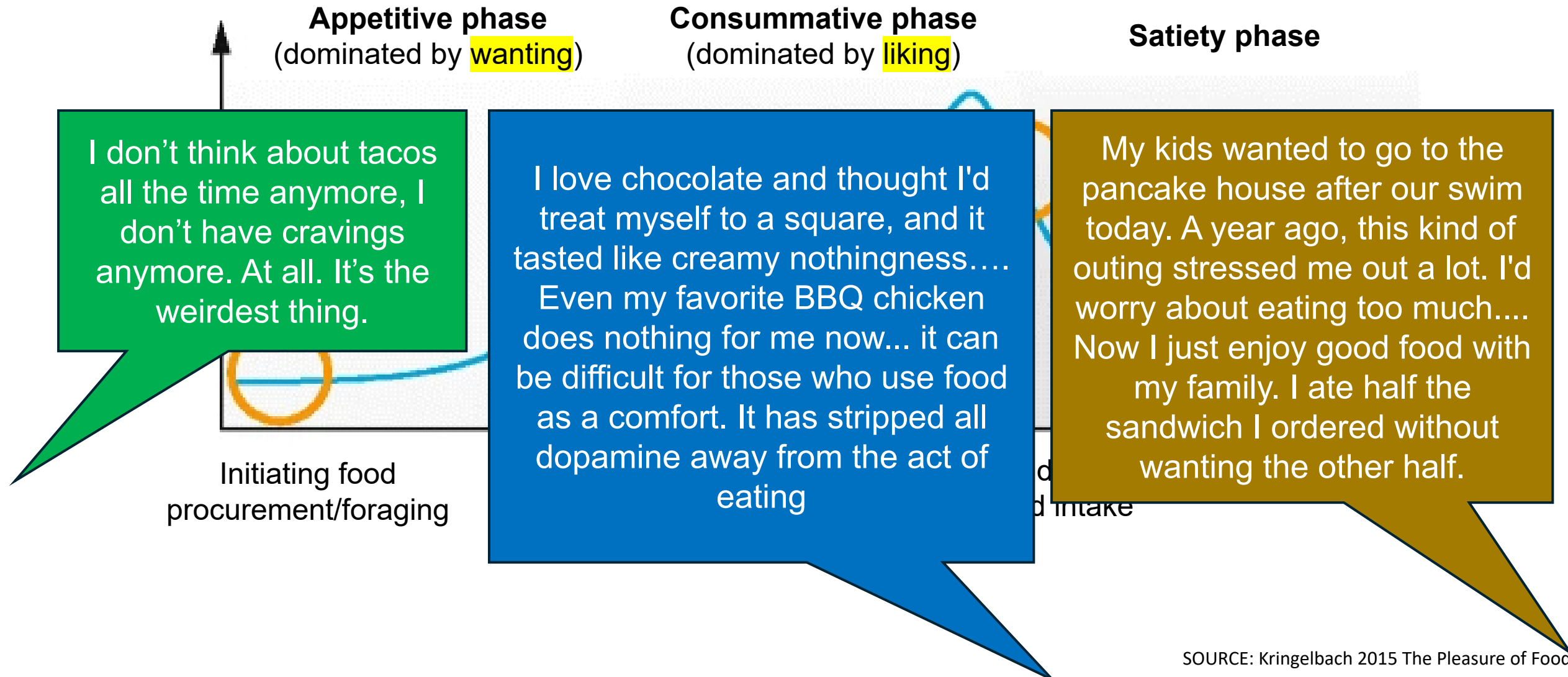


Conclusion: **Stress**, **cravings**, and **negative mood** are increasing prior to use events

Treatment entry

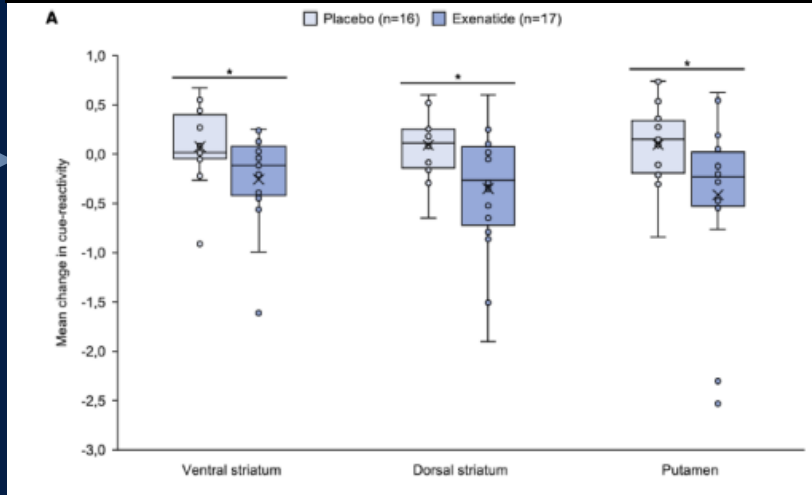


Pleasure Cycle

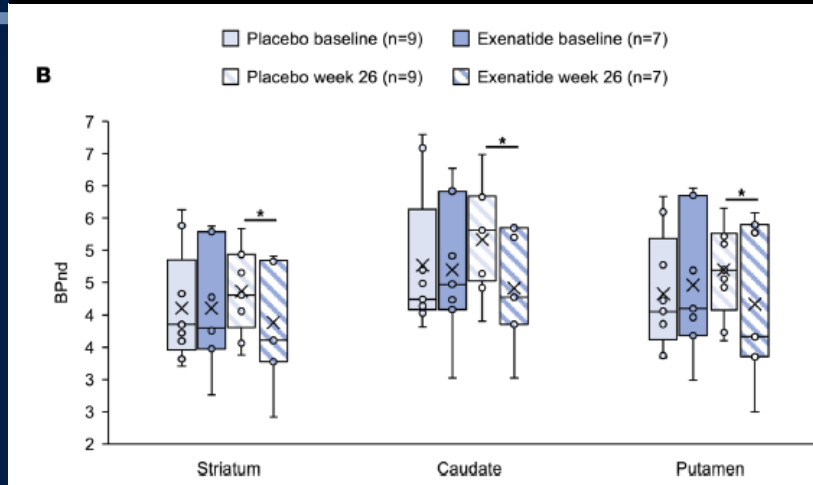


Treatment entry

Cue-reactivity lower in those receiving exenatide



Dopamine transporter availability lower in those receiving exenatide



Regulation of cravings and negative affect

GLP-1RA improve regulation, increasing satiety?

Stress-induced cravings

Cravings ("Wanting")

Relapse ("Liking")

Cue-induced cravings

Drug-induced cravings

GLP-1RA attenuate the "wanting" of substances, increasing satiety?

GLP-1RA attenuate the "liking" of substances, increasing satiety?

Clinical trials at Brigham and Women's Hospital being launched

Semaglutide for the treatment of OUD

- NIDA R21 (DA060304)
- 12-week, double-blind, placebo-controlled, randomized trial of individuals with OUD to receive either weekly injections of semaglutide or placebo.
- Recruit individuals (n=40) recently initiating SL buprenorphine treatment
- **Aim 1:** Determine the effects of semaglutide on opioid cue-reactivity.
- **Aim 2:** Assess the safety and preliminary efficacy of semaglutide for OUD

Tirzepatide for the treatment of AUD

- Institutional award (McGraw Innovator Award)
- Pilot, 4-week, double-blind, placebo-controlled, randomized trial of individuals with AUD to receive either weekly injections of tirzepatide or placebo.
- Recruit individuals (n=20) completing inpatient withdrawal treatment at an ASAM level 4 unit
- **Aim 1:** Determine the effects of tirzepatide on alcohol cue-reactivity.
- **Aim 2:** Assess the safety and preliminary efficacy of tirzepatide for severe AUD

Summary of GLP-1RAs

- GLP-1RAs have been available for 20 years, providing some reassurance for their safety
- Dual (GIP) and triple (Glucagon) agonists emerging, potentially with greater efficacy and safety
- Population-level evidence in support of GLP-1RAs reducing substance use
- Reduced “wanting”, reduced “liking” as well as increased “satiety” are possible mechanisms by which GLP-1RAs reduce substance use
- Randomized clinical trials are needed