# GLP-1 Agonists for Addiction

**Joseph Merrill MD MPH**
Professor of Medicine
University of Washington

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No conflicts of interest to disclose.

# Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

# GLP-1 Agonists for Addiction

- Much of this talk is taken from presentations or references in talks at the 56th Annual American Society of Addiction Medicine meeting, specifically by:
  - Stephanie T. Weiss, MD, PhD, MS
  - Jeffrey Brent, MD, PhD
  - Joji Suzuki, MD
  - Sarah E. Wakeman, MD
  - Luba Yammine, PhD, APRN, FNP-C

- I will be discussing the off-label use of GLP-1 agonists for treatment of addiction.

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# Addiction and HIV

- Substance use disorders are common among those with or at risk for HIV
- Effective medication for opioid, alcohol, and tobacco use disorders are available, but are under-prescribed
- Providers have variable knowledge of and experience with medications for substance use disorders
- GLP-1 agonists are now commonly prescribed for a variety of indications, making them more likely to be used widely if shown effective for addiction

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# Glucagon-like Peptide-1 Receptor Agonists

- Yes, first found in Gila monster venom!
- Release insulin but short (1-2 minute) half-life
- Initial research aimed to lengthen half-life, resist degradation and enhance receptor binding
- Acts in brain, pancreas, stomach, intestines, liver
- Increases satiety

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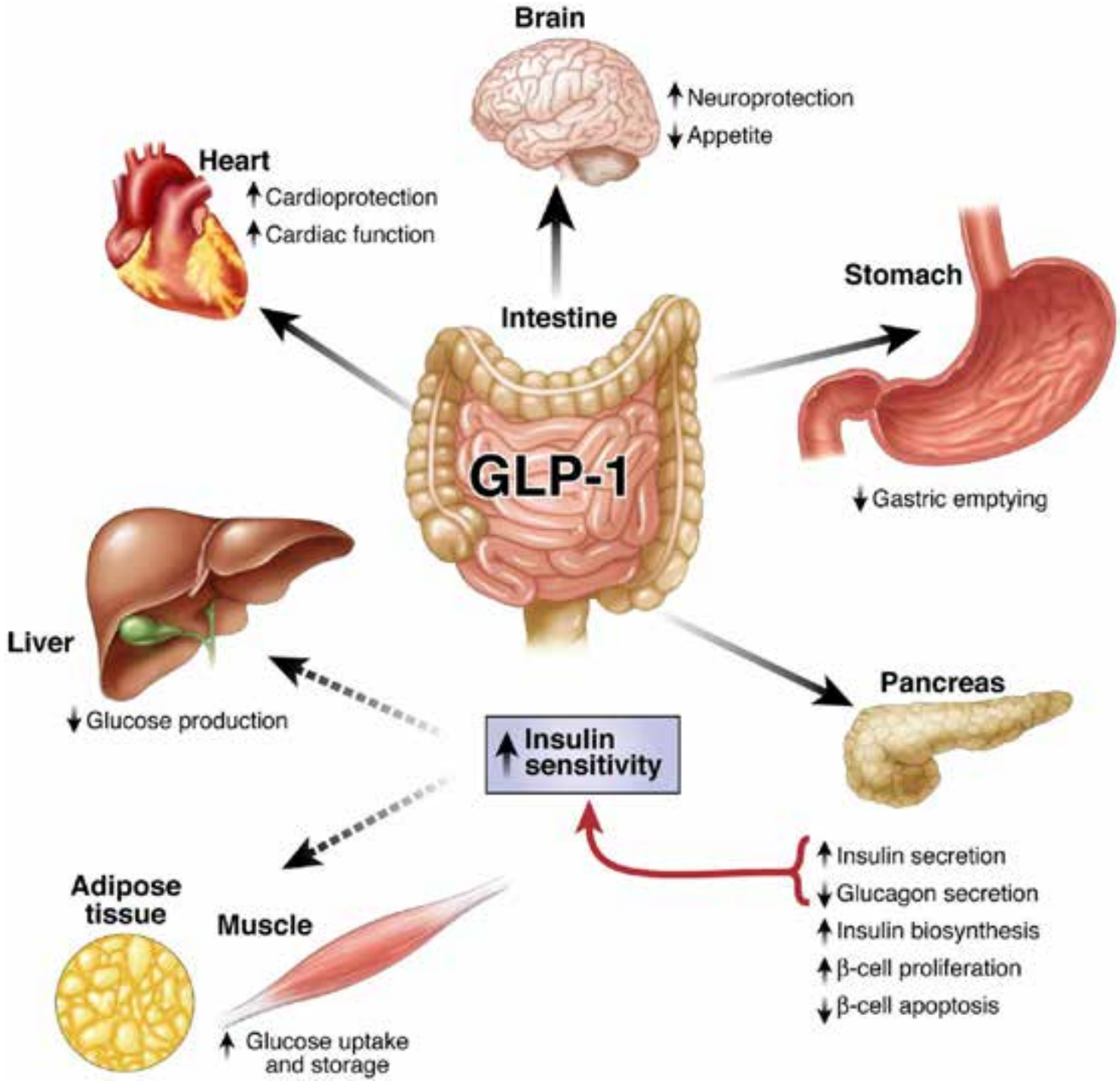
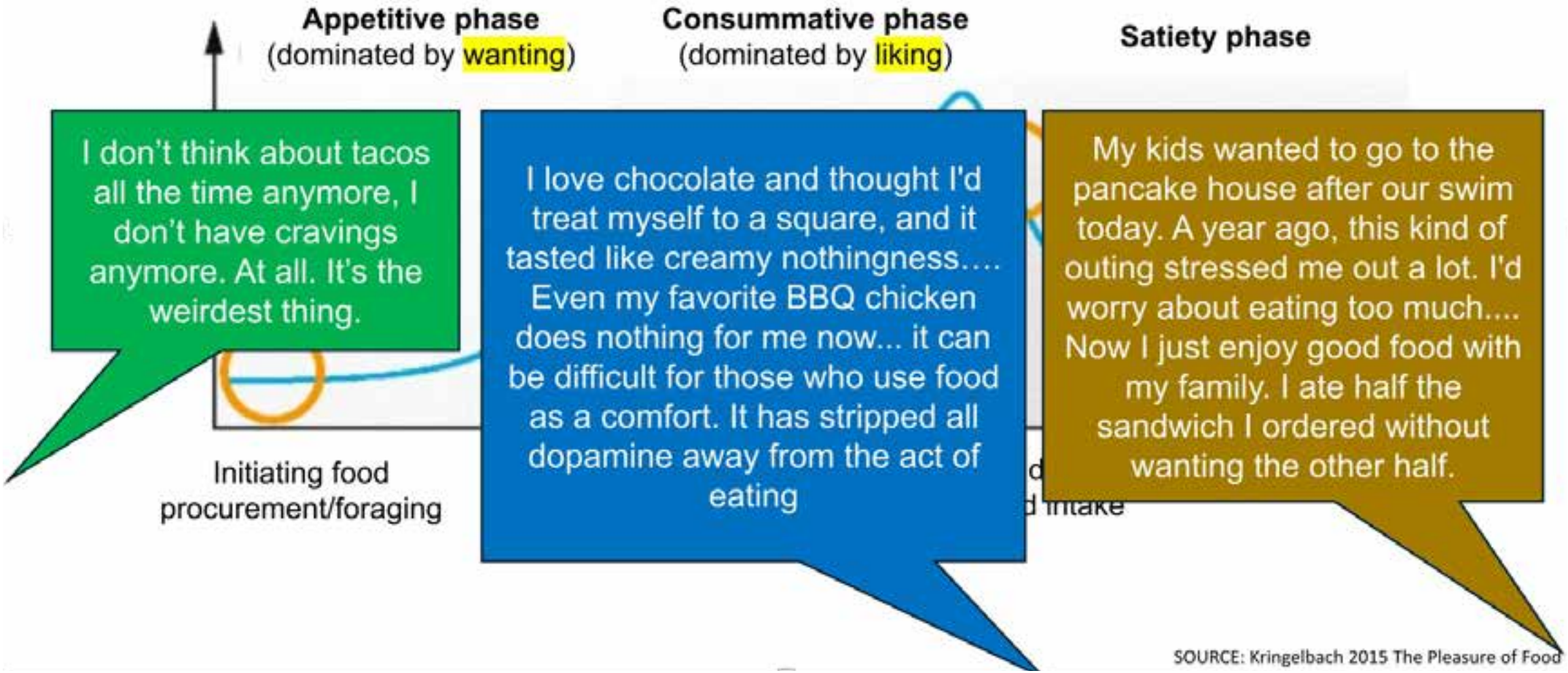
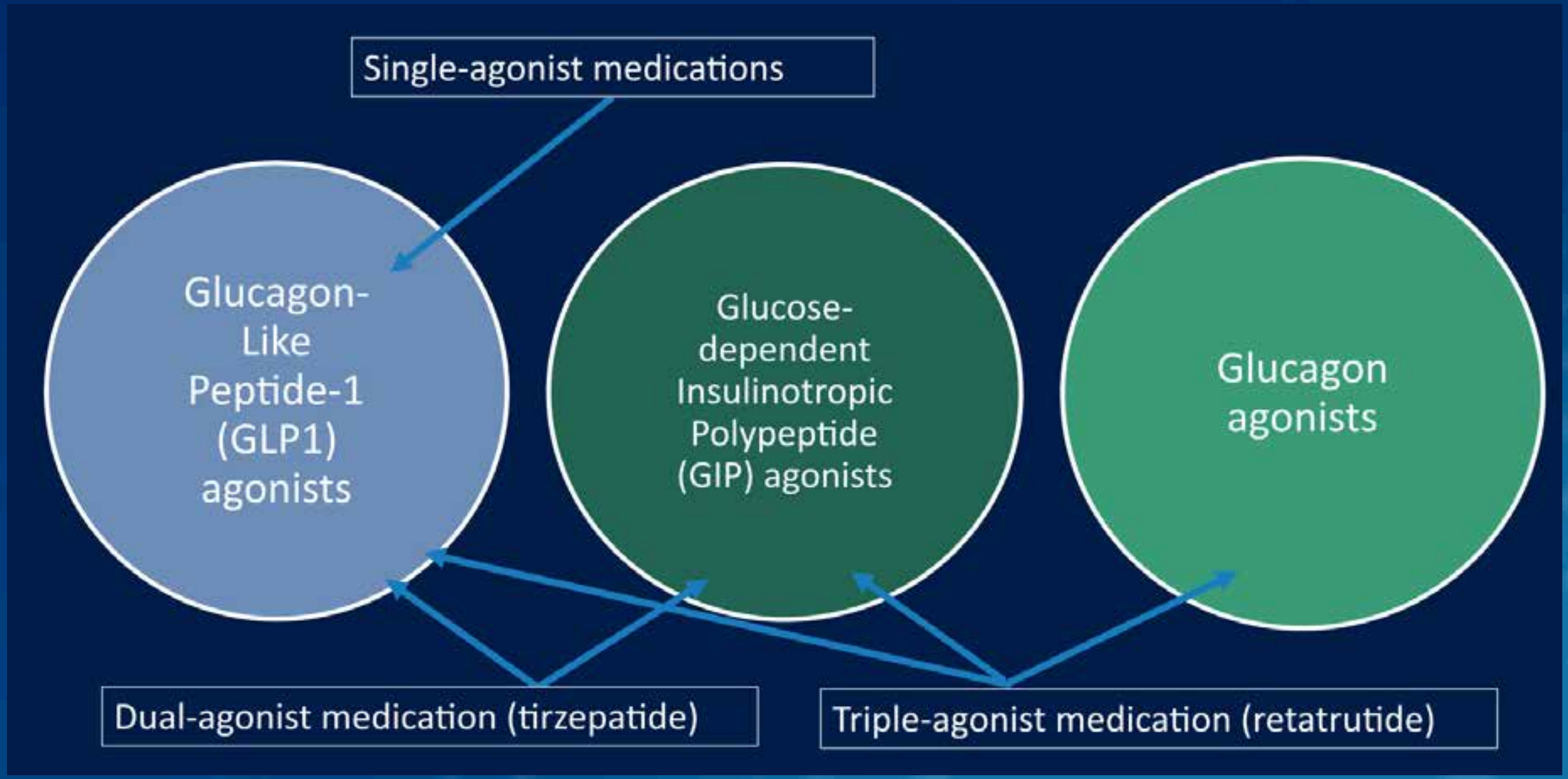
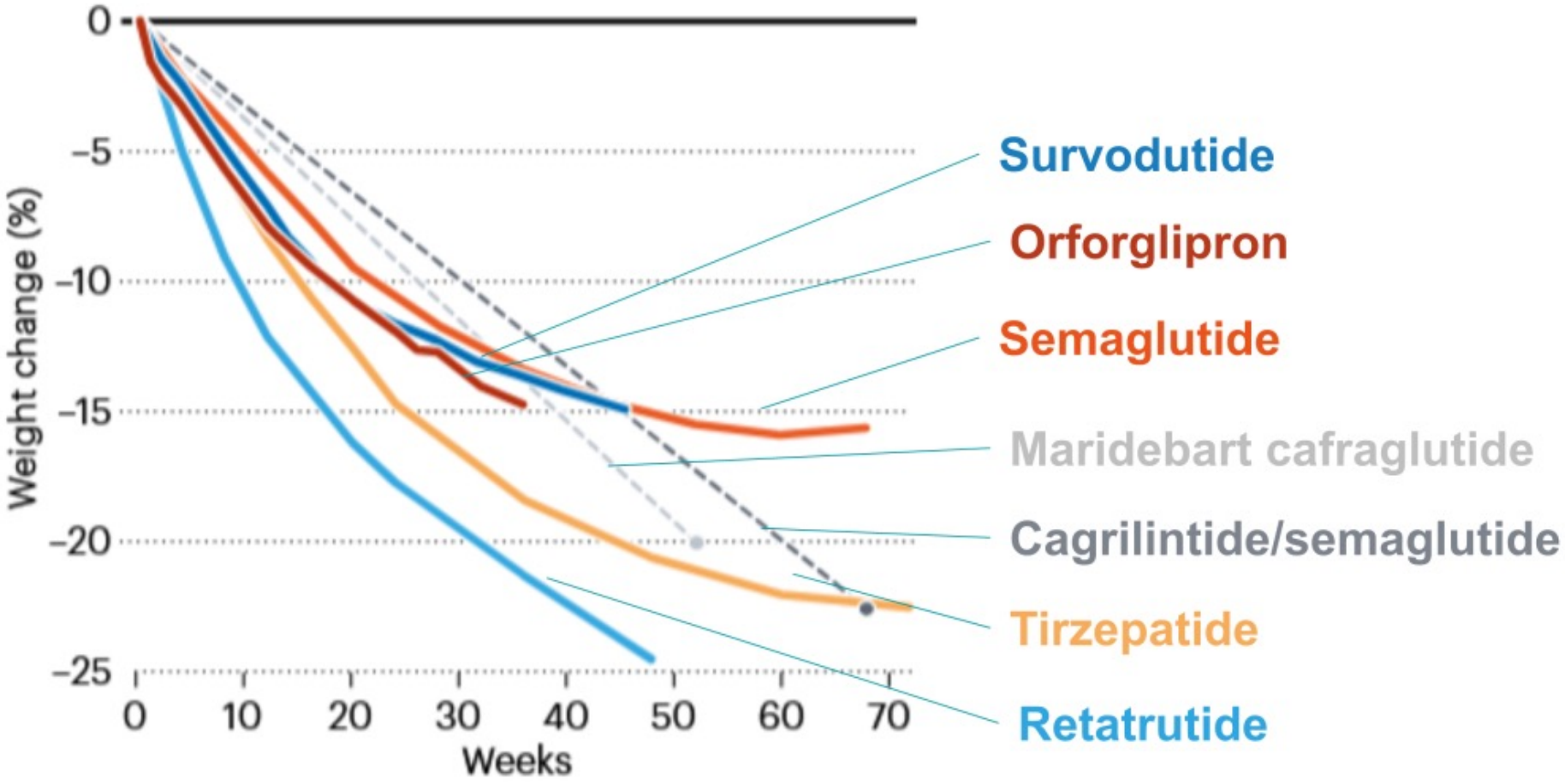

Brain
↑ Neuroprotection
↓ Appetite
Heart
↑ Cardioprotection
↑ Cardiac function
Intestine
GLP-1
Stomach
↓ Gastric emptying
Liver
↓ Glucose production
Pancreas
↑ Insulin sensitivity
↑ Insulin secretion
↓ Glucagon secretion
↑ Insulin biosynthesis
↑ β-cell proliferation
↓ β-cell apoptosis
Adipose tissue
Muscle
↑ Glucose uptake and storage

# Pleasure Cycle




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)

# Newer GLP-1/GIP/GA Medications




*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.

Dolgin 2025 Nature

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# GLP-1 Agonist Use

- One or more GLP-1 agonists are approved for type 2 diabetes, obesity, CV risk reduction, kidney disease, sleep apnea
- One in eight adults have used GLP-1 drugs
  - 43% of those with diabetes
  - Frequently not covered for other indications
- Not approved for addiction
  - Preclinical evidence in mice, rats, primates

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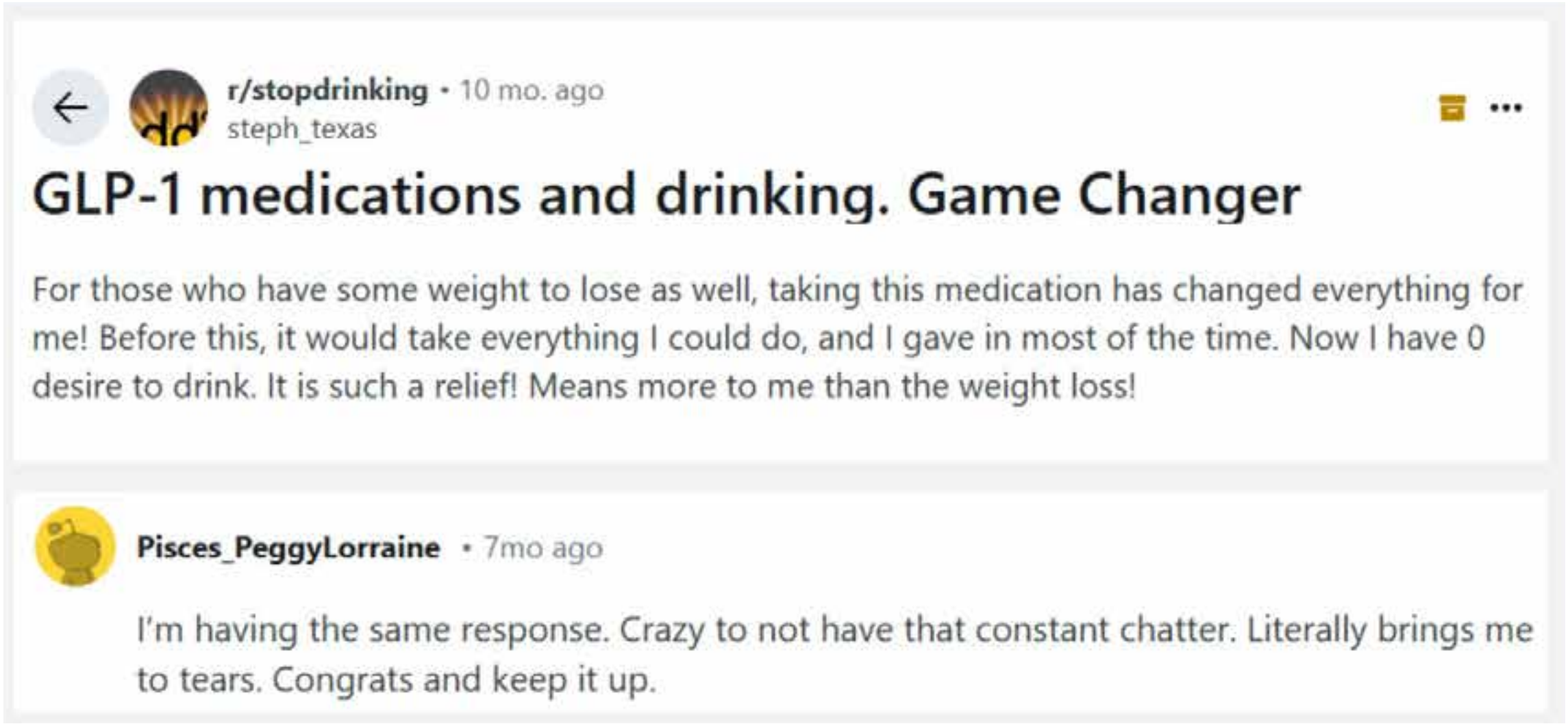
# Anecdotal Experience of Reduced Alcohol and Other Substance Craving



r/stopdrinking • 10 mo. ago
steph_texas

## GLP-1 medications and drinking. Game Changer

For those who have some weight to lose as well, taking this medication has changed everything for me! Before this, it would take everything I could do, and I gave in most of the time. Now I have 0 desire to drink. It is such a relief! Means more to me than the weight loss!

**Pisces_PeggyLorraine** • 7mo ago

I'm having the same response. Crazy to not have that constant chatter. Literally brings me to tears. Congrats and keep it up.

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# GLP-1 Agonists for Alcohol Use Disorder

- Evidence is limited
- Anecdotal reports
- Epidemiologic studies
- Randomized trials
  - Few published placebo-controlled trial
  - Other trials underway

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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

- Large Swedish observation cohort study
- Evaluated whether AUD patients prescribed GLP-1 agonists had lower AUD/SUD hospitalization risk when taking GLP-1 agonists vs when not taking

A Risk of somatic hospitalization associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

| Drug | No. Users | Events | PYs | aHR (95% CI) |
|---|---|---|---|---|
| GLP-1 agonists | | | | |
| Exenatide | 98 | 50 | 167 | 0.70 (0.46-1.06) |
| Semaglutide | 4321 | 708 | 4677 | 0.78 (0.68-0.90) |
| Liraglutide | 2509 | 613 | 3076 | 0.79 (0.69-0.91) |
| Dulaglutide | 1118 | 362 | 1443 | 0.92 (0.76-1.12) |
| AUD medications | 75454 | 9995 | 73222 | 0.85 (0.83-0.88) |

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# Cohort Study of GLP-1 Agonists for AUD

- Provides additional rational for testing GLP-1 agonists for AUD treatment
- Bias in comparison of GLP-1 agonists and AUD medications would be present if:
  - AUD medications were prescribed at a time of worsening AUD, or if:
  - GLP-1 agonists were initiated at a time of AUD stability
- Both biases are plausible
- Placebo and comparative trials are needed

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# GLP-1 Agonists in HIV

- Observational data from CNICS clinics assessed changes in alcohol use in patients with HIV and baseline alcohol use
- Those prescribed semaglutide for diabetes or obesity had lower levels of alcohol use at follow-up, especially those with higher AUDIT-C scores at baseline
- A separate published CNICS study found racial differences in semaglutide prescribing, highlighting the limits of observational data

Crane HM, et al. The Impact of Semaglutide on Alcohol Use Among People with HIV in Routine Clinical Care in the US. Poster presentation at CROI 2025 Poster #1152.
Hahn AW, et al. Racial Inequity in Prescription of Semaglutide Among Eligible People With HIV. Diabetes Care. 2025 Oct 1;48(10):1761-1765. doi: 10.2337/dc25-0236. PMID: 40971637; PMCID: PMC12451842.

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# Exenatide for Alcohol Use Disorder

- Placebo-controlled trial of exenatide for 26 wks
- AUD and 5 heavy drinking days/mo (N=127)
- Both groups got CBT
- Result showed no difference in heavy drinking days – both groups improved
- Exploratory analysis showed reduced heavy drinking in sub-set with BMI > 30

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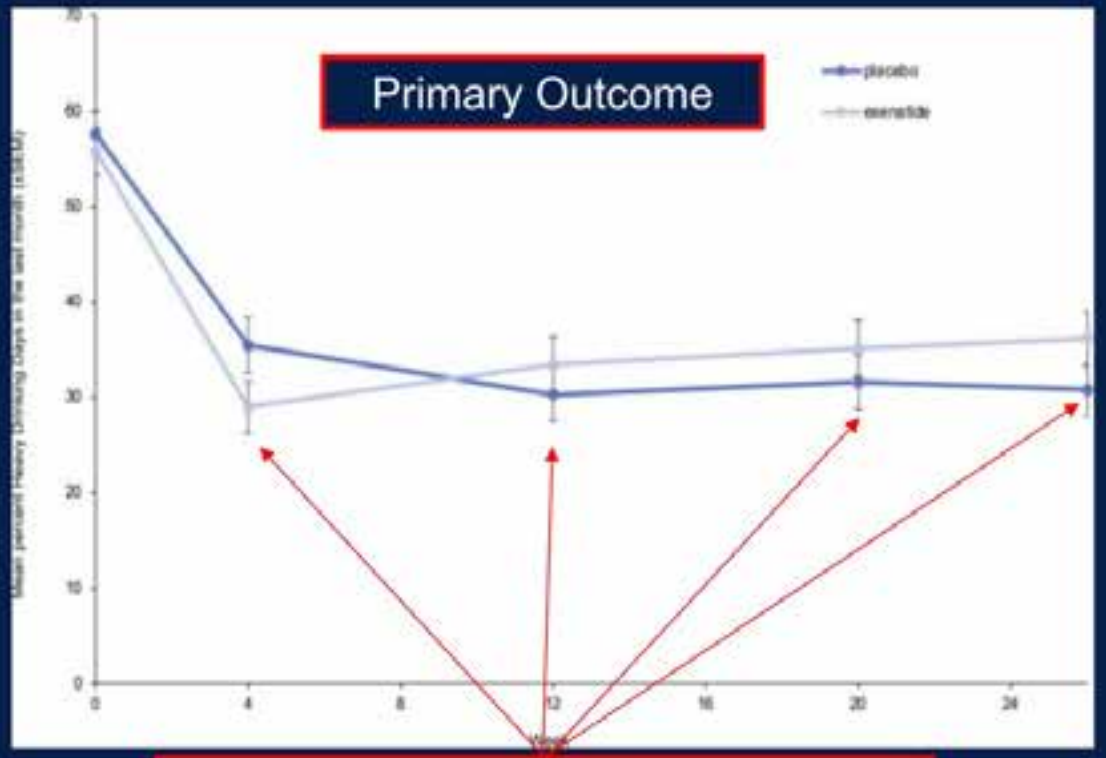
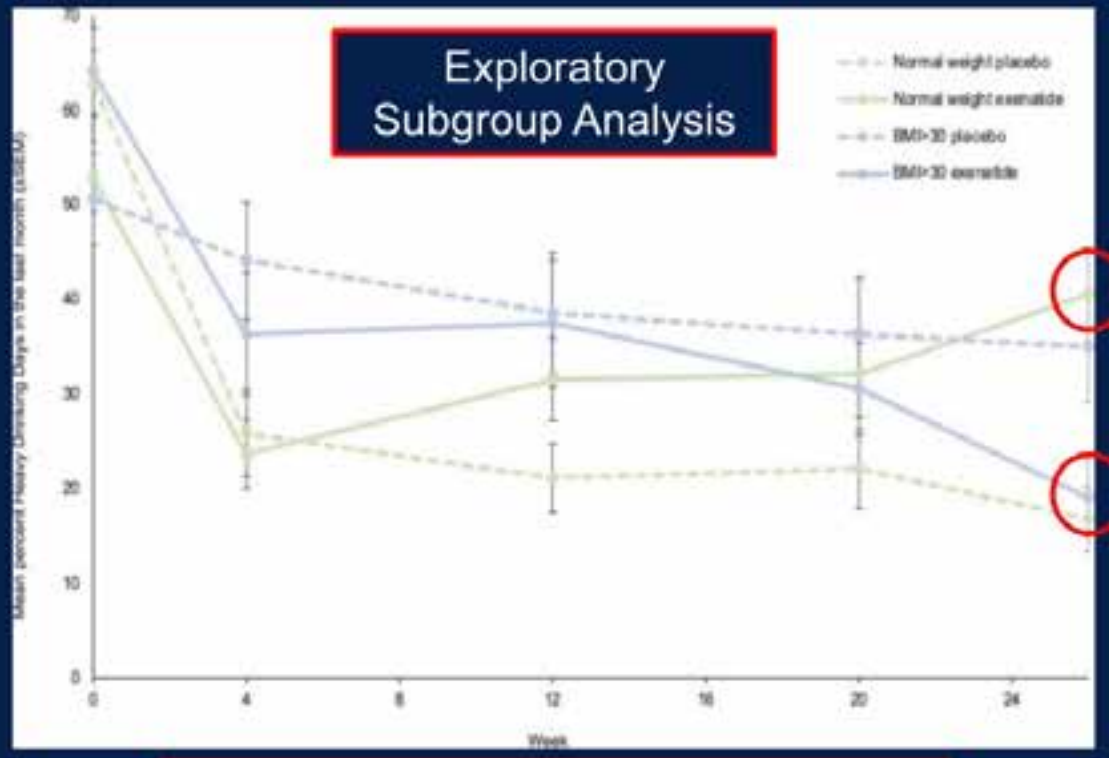
# First Published Trial of GLP-1RA in AUD




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

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# Semaglutide RCT for Alcohol Use Disorder

- Phase 2, placebo-controlled trial of weekly semaglutide in 48 “non-treatment seeking” adults with AUD
- Dose increased Q4 weeks to 1.0 mg after week 8
- Primary outcome was alcohol self-administration in a lab setting before treatment and after 9 weeks
- Results favored semaglutide with medium-large effect
- Did not impact drinks/day or #days drinking, but reduced drinks/drinking day, heavy drinking days, craving, and among smokers, cigarette use

Hendershot CS, et al. Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2025 Apr 1;82(4):395-405.

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# 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*

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# 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 consnmed | 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 |

Clinicaltrials.gov; Henderson et al. (2023) JAMA Psychiatry

# 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.

# GLP-1 for Smoking Cessation – Epi Studies

- Analyses of EHR data from patients with type 2 diabetes (T2D):
  - Compared to patients who used other medications for T2D, patients who used GLP-1RA were less likely to receive a diagnosis of nicotine misuse
  - In patients with T2D and comorbid tobacco smoking - compared to patients who used other medications for T2D, GLP-1RA use was associated with less healthcare utilization for tobacco use disorder

SOURCE: 9.De Giorgi et al (2024)
10.Wang et al (2024)

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# GLP-1 Agonists for Smoking Cessation

- Exenatide 2mg once weekly adjunct to nicotine patch X 6 weeks (n=84)
  - Abstinence: exenatide 46.3%, placebo 26.8%
  - **Post-cessation body weight: exenatide -0.22 kg, placebo +1.3 kg**
- Dulaglutide 1.5 mg once weekly adjunct to varenicline X 12 weeks (n=255)
  - Abstinence: dulaglutide 63%, placebo 65%
  - **Post-cessation body weight: dulaglutide** -1kg [SD=2.7]), placebo +1.9kg [SD=2.4]
- Semaglutide once weekly X 8 weeks (0.25 mg X 4 weeks, 0.5 mg X 4 weeks)
  - Greater declines in cigarettes per day in the semaglutide group vs. placebo
  - **Change in body weight: semaglutide -5.05%, placebo +0.18%**

SOURCE: 6. Yammine et al (2021)
7. Lengsfeld et al (2023)
8. Hendershot et al (2025)

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# GLP-1 Agonists for Smoking Cessation

- **NCT05530577**: Semaglutide once weekly up to 1 mg/week X 9 weeks (n=48)
- **NCT03712098**: Daily liraglutide 3 mg/day X 32 weeks (n=40)

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# Ongoing Studies

- **NCT05610800:** A Randomized Controlled Trial of Exenatide as an Adjunct to Nicotine Patch for Smoking Cessation and Prevention of Post-Cessation Weight Gain (R01 DA053241; PI: Yammine, Co-PI: Verrico)

- **NCT06173778:** A Randomized Controlled Trial of Once-Weekly Semaglutide for Limiting Post-Smoking Cessation Weight Gain in Adult Smokers with Overweight/Obesity (Novo Nordisk Investigator Initiated Trial; PI: Yammine, Co-PI: Leidy)


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# In Summary

- Promising preclinical and epidemiological data
- Completed RCTs are few: different GLP-1RAs/smoking cessation medications; different study populations
- Consistently positive impact on preventing weight gain in the context of smoking cessation
- Further clinical research is needed

# GLP-1 Agonists for Addiction

- Promising but unproven benefits for a range of substance use disorders
- Anecdotal and epi data are encouraging
- RCTs are underway
- All providers are learning how to use them and are seeing their benefit
- Stay tuned!

# Acknowledgment

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