ECHO IDAHO

Behavioral Health in Primary Care

State of the Science: GLP-1s and Behavioral Health

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Tara Whitaker, MD

ECHO Behavioral Health Panelist

ECHO Idaho, St. Luke's Health System

University of Idaho
School of Health and Medical Professions

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Learning Objectives

- Review current data on mental health risks and benefits of GLP-1 receptor agonist medications such as semaglutide and tirzepatide
- Compare mental health effects of GLP-1 medications to other weight loss medications and interventions
- Review emerging evidence for GLP-1 medication use in alcohol use disorder and other substance use disorders
- Discuss current understanding of impacts on eating disorders
- Outline areas of emerging research

It’s Early Days….

- Some conflicting data on mental health effects of GLP-1 receptor agonists
- Overall data is reassuring that mental health risk is low
- However, pharmacovigilance databases have continued to show increase suicidality and depressive symptoms
  - These may reflect “real world” use
  - But, these rely heavily on patient and clinician reporting which is known to have bias or not be representative of a truly randomized sample
- Key limitation of randomized controlled trials:
  - Majority of major trials **excluded** patients with:
    - major depressive disorder (PHQ ≥15)
    - unstable psychiatric illness
    - prior suicide attempt

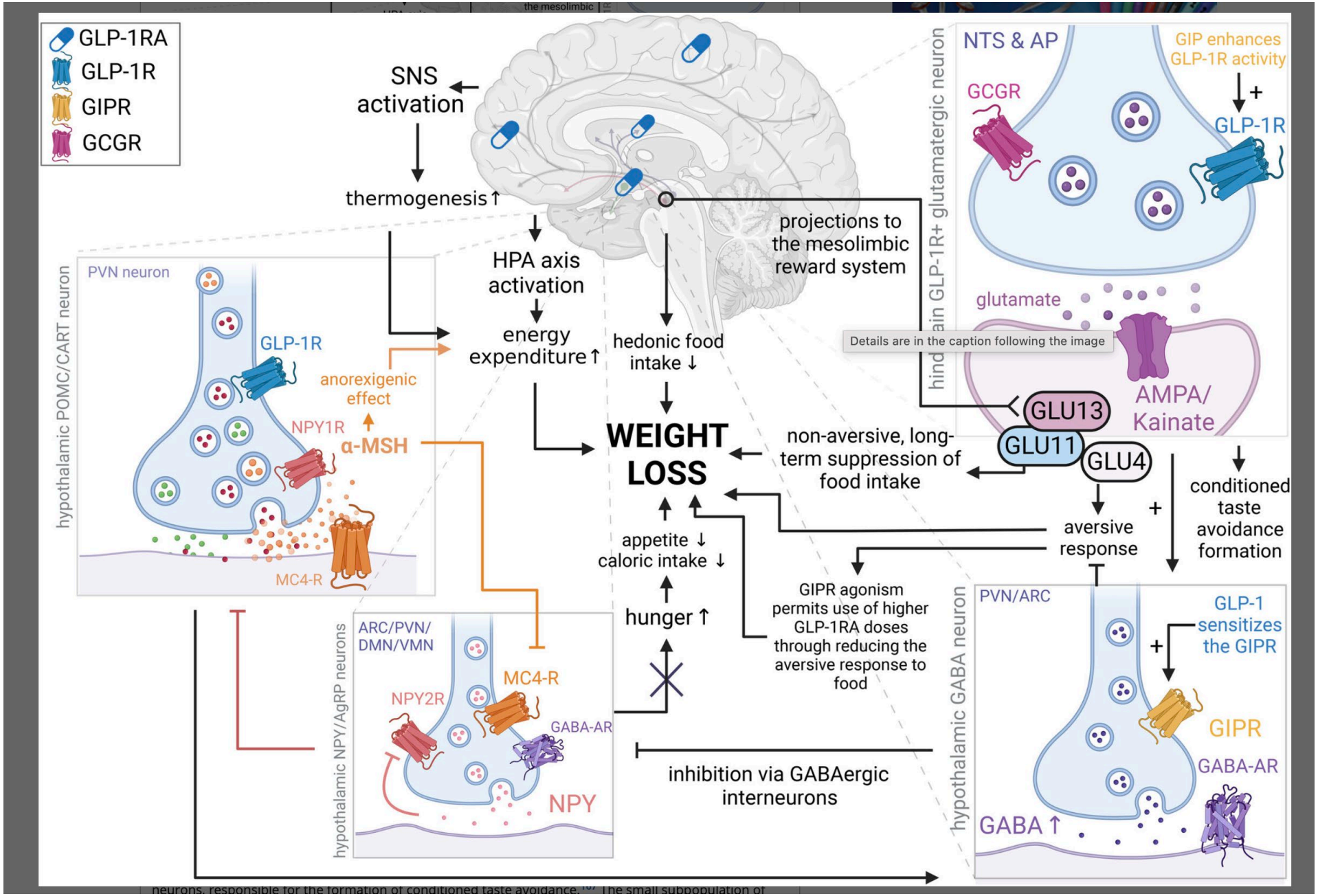
Pharmacovigilance database data

- Disproportionate reporting of suicidal ideation and depressed mood with semaglutide
  - WHO VigiBase
  - Suggestion of “Weber effect” (predictable sharp spike in reporting of adverse events for new medications) since reporting went up significantly following approval of semaglutide for weight loss
  - Antidepressant use was 2.3 to 5 times more likely among GLP-1 RA reporters, indicating possible confounding or….
    - Are individuals with depression vulnerable to adverse psych effects?

Glucagon-Like Peptide 1 Receptor Agonist and Mental Health: Systematic Review and Meta-Analysis

JAMA Psychiatry May 2025

- 80 randomized clinical trials involving 107,860 patients were included in this meta-analysis
- Compared to placebo, GLP-1 RA treatment **was not** associated with:
  - Risk of serious adverse psychiatric events
  - Increased risk of self harm or suicidality
  - Non-serious psychiatric adverse events
  - Depressive symptom change compared to placebo
- GLP-1 RA treatment **was** associated with:
  - improvements and restrained eating and emotional eating behavior
  - mental health and physical health-related quality of life,
  - diabetes-related quality of life
  - weight-related quality of life compared to placebo
- Limitations:
  - Studies did not collect data on a broader range of psychiatric symptoms, including energy, sleep, or obsessional symptoms.
  - Exclusion criteria included, pre-existing serious psychiatric diagnoses, major depressive disorder, suicidality and binge-eating disorder



Functional MRI research has revealed likely mechanisms of action of GLP-1 RA activity.

Receptors are located throughout the brain.

Aliment Pharmacol Ther, Volume: 59, Issue: S1, Pages: S52-S75, First published: 30 May 2024, DOI: (10.1111/apt.17848)

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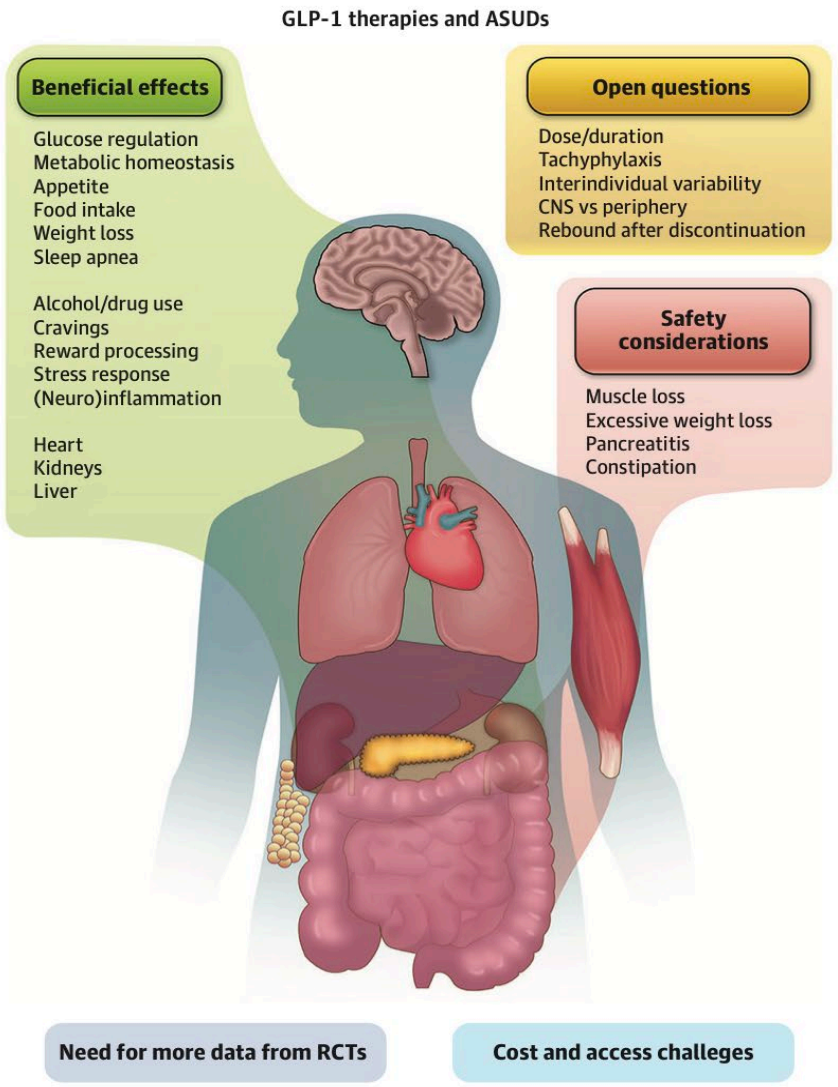
For comparison:
Psychiatric Effects of Weight Loss Pharmaceuticals

- Weight loss drugs
  - Phentermine: CNS stimulant (agitation, anxiety, abuse potential)
  - Phentermine – topiramate:
    - most extensive psychiatric warning profile
    - twice the risk of suicidal thinking and behavior
    - cognitive impairment
  - Naltrexone– bupropion:
    - mild improvement in depression, attributed to bupropion
    - insomnia and anxiety scores were higher
    - Contraindicated in drug and alcohol withdrawal due to bupropion component.
  - Orlistat: lowest potential for psychiatric side effects, use limited by physical side effects

For comparison: Psychiatric Effects of Weight Loss Surgeries

- Effects are generally more pronounced in gastric bypass vs gastric sleeve
  - Improved depression overall, especially early in course
  - Overall signal of improved anxiety
  - Suicide risk elevated
  - Alcohol use disorder risk elevated
  - Non-alcohol substance use risk increased with gastric bypass
  - Improved binge eating
  - Improved body image

Figure. Current Landscape and Main Beneficial Effects, Safety, Considerations, and Open Questions and Challenges With Glucagon-Like Peptide-1 (GLP-1) Therapies in Relation to Alcohol and Other Substance Use Disorders (ASUDs)



CNS indicates central nervous system; RCT, randomized clinical trial.

GLP-1 RAs show promise in direct treatment of addiction and psychiatric illness—Early days

- The improvement in mental health quality of life did not correlate with the magnitude of weight loss or hemoglobin A1c change
  - Possible direct mechanism through central nervous system
- However, use of GLP-1 RAs is in the setting of addiction is in very early stages of research.
  - Unknown:
    - Dose
    - Duration of treatment
    - Impact of discontinuation
    - Individual differences
    - Prediction of response
    - Mechanism of action
    - Intersection of mental and medical health comorbidities
  - Barriers:
    - Cost
    - Fair access

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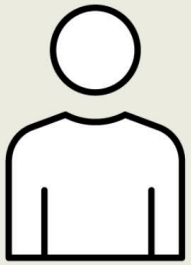
RCT: Once-Weekly Semaglutide in Adults with Alcohol Use Disorder

POPULATION

14 Men, 34 Women



Non–treatment-seeking adults meeting criteria for alcohol use disorder

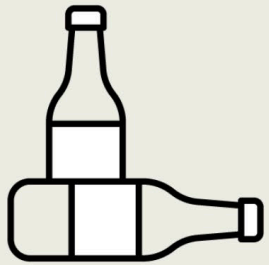
Mean (SD) age, 39.9 (10.6) y

SETTINGS / LOCATIONS

1 US academic medical center

INTERVENTION

48 Participants randomized and analyzed



24 Semaglutide
Once-weekly semaglutide

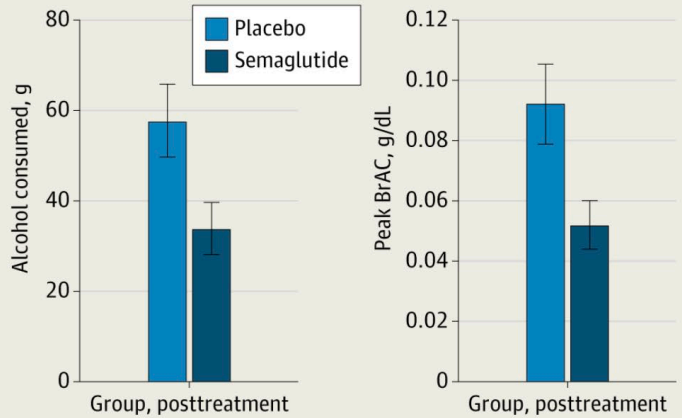
24 Placebo
Placebo injections

PRIMARY OUTCOME

Estimated alcohol consumed over 120 min during laboratory self-administration (estimated alcohol consumed in grams and peak breath alcohol concentration [BrAC] in g/dL)

FINDINGS

Among participants consuming alcohol in a laboratory session following 8 wk of treatment, those in the semaglutide group drank significantly less alcohol than those in the placebo group



Mean (SD) alcohol consumed: Semaglutide: 33.62 (20.72) g; placebo: 57.19 (28.15) g
Mean (SD) peak BrAC: Semaglutide: 0.052 (0.029) g/dL; placebo: 0.092 (0.046) g/dL
Effect sizes: Alcohol consumed: β, −0.48; 95% CI, −0.85 to −0.11; *P* = .01; peak BrAC: β, −0.46; 95% CI, −0.87 to −0.06; *P* = .03

Hendershot CS, Bremmer MP, Paladino MB, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. Published online February 12, 2025. doi:10.1001/jamapsychiatry.2024.4789

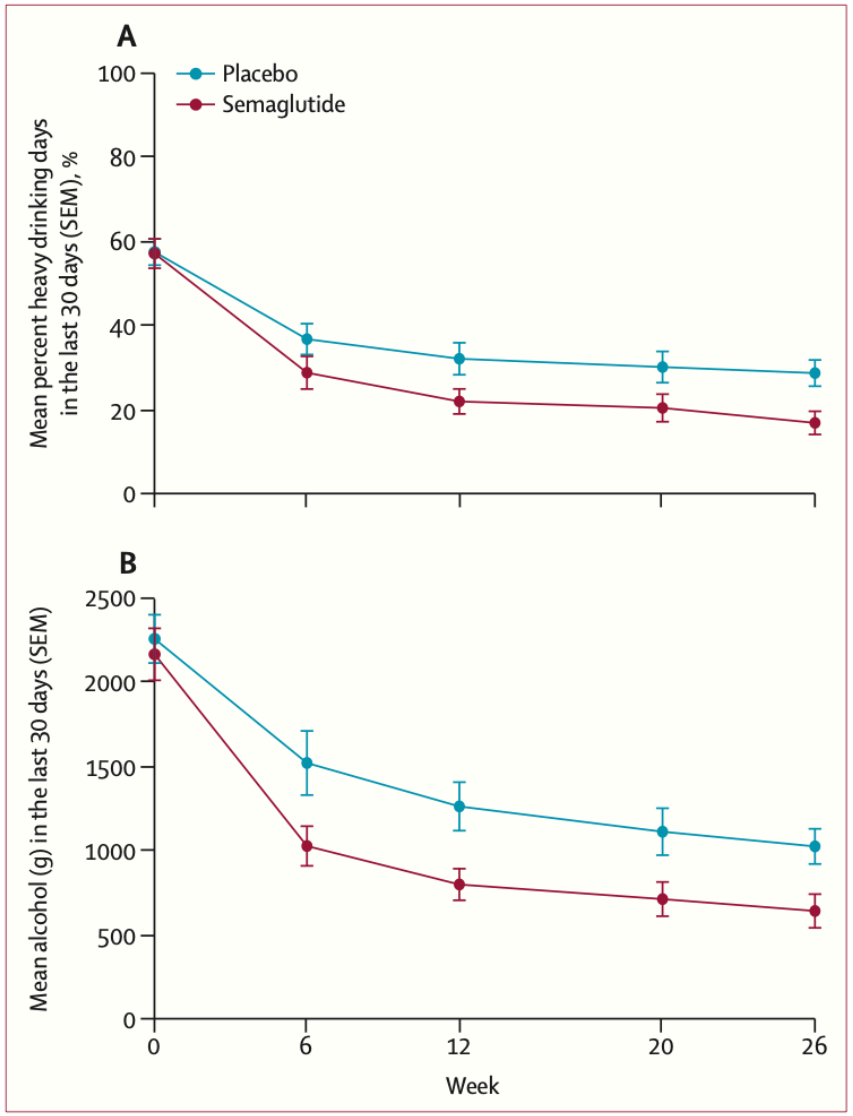


Figure 2: **Effects of once-weekly semaglutide compared with placebo on reduction in heavy drinking days and total alcohol consumption**
Changes from baseline (week 0) to follow-up (week 26) are shown for mean percent heavy drinking days in the last 30 days (A), and mean alcohol (g) consumed during the past 30 days (B), in participants randomly assigned to semaglutide 2·4 mg (n=54) or placebo (n=54). Participant level changes by treatment group are in appendix 2 (p 15). SEM=standard error of the mean.

Klausen et al. *Lancet* 2026
26-week RCT
108 participants
Alcohol Use Disorder plus Obesity
Semaglutide had significant impact compared to placebo mainly by reducing heavy drinking days with an NNT of 4.3

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Eating disorders and GLP-1s

- Future study needed, but emerging patterns are recognized
- Promising therapeutic potential for binge eating disorder
  - Meta-analyses have shown:
    - Reduction in “emotional eating” and increased in “restrained eating” with GLP-1 RAs
    - Reduction in binge-eating with liraglutide
  - 2026 American Diabetes Association guidelines
    - "may have relevance to the treatment of disrupted or disordered eating"
- Restrictive eating disorder is a relative contraindication for GLP-1 therapy
  - Reinforcement of restriction, eating avoidance, compulsive weight control
  - Risk of fear of eating, induced vomiting
- Eating disorder screening should be part of all GLP-1 evaluations
  - If noted history, referral to obesity medicine specialty care and eating disorder support is warranted
- Significant level of unsupervised use is posing elevated risk

Future directions

- Alcohol use disorder
  - Multiple ongoing RCTs as noted, large confirmatory trials anticipated
- Major Depression Treatment
  - Improved decision-making
  - Improved anhedonia
- Other SUDs
  - Preclinical data promising for:
    - Opiate use disorder
    - Tobacco use disorder
    - Cocaine use disorder
- Schizophrenia, spectrum disorder
  - Showing promise in antipsychotic induced metabolic dysfunction
  - No demonstrated consistent effects on psychiatric symptomology

Key Points

- Risk to mental health from GLP-1 RAs and GLP-1/GIP medications appears minimal
- In comparison to other weight loss interventions, risk appears lower
- GLP-1 RAs show promise in alcohol and substance use disorders, though additional research is needed
- There appears to be a beneficial effect on binge eating disorders, but significant risk exists to patients with restrictive eating disorders
- Additional research is needed, but new applications are expected

References

Available on request