

GLP-1/GIP treatments for the Opioid Epidemic?



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Tirzepatide and Semaglutide : New Frontier in Substance Use Disorder (SUD) Treatment

Emerging Clinical Trials and Therapeutic Potential

Conclusions up Front

- Tirzepatide and semaglutide show treatment potential across multiple substance classes (Alcohol, Opioids, Stimulants, Nicotine).
- Early observational data needs confirmation with pilot Phase II trials and Phase 3 formal randomized trials
- Potential for a "dual-win": Treating addiction while simultaneously managing metabolic health
- Future research is needed to determine the safety and ideal dosing specifically for SUD patients

We all know the scope of the problem.

What we are looking for is hope.

Clinical stories:

- ‘I began Ozempic to lose weight, after a few months I realized I was buying a lot less smokes, drinking less too.’
- ‘I don’t crave snacks anymore and I think it has helped me cut down drinking in the evenings. ‘

Where are we at with the science?

- Start with observations that might be true
- Perform animal studies to understand biology of condition
- Review existing data that systematically look at interventions and outcome
- Postulate at plausible biologic mechanism to explain the association
- Randomized, prospective, placebo-controlled trials (efficacy and safety)
- Monitor for uncommon side effects and adverse events (safety)

Peptides: what are they?

- Peptides are short chains of amino acids (typically 2–50) that act as essential messengers, instructing cells to perform specific functions
- **Signaling molecules**, instructing cells to perform tasks like repairing tissue, regulating metabolism, or producing hormones
- Common examples include [insulin](#) (for blood sugar) and [oxytocin](#)

Understanding the Mechanism: GLP-1 and GIP

- GLP-1 receptor agonists (Glucagon-Like Peptide 1 e.g., semaglutide)
 - Secreted in the gut and brain.
 - Promotes insulin, slows gastric emptying, and signals satiety.
- Dual GLP-1/GIP agonists (adding GIP or Glucose-dependent Insulinotropic Polypeptide e.g., tirzepatide)
 - Works with GLP-1 to manage postprandial insulin.
 - Stimulates glucagon at low glucose levels to prevent "crashes"
- Synergy: Drugs like Tirzepatide activate both receptors, potentially offering a more robust effect on metabolic and reward pathways than GLP-1 alone.

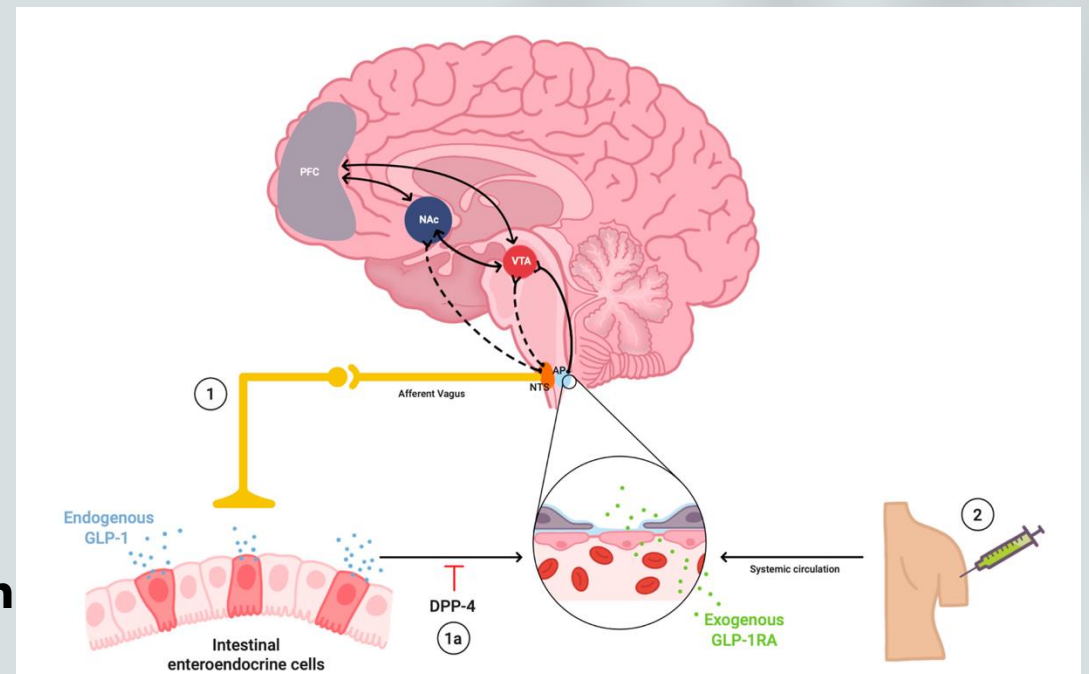
Beyond the Pancreas: The Brain's Reward Center

- Targets: Nucleus Accumbens (NAc) and Ventral Tegmental Area (VTA).
- Dopamine Modulation: GLP-1 RAs modulate dopamine signaling, the chemical "currency" of reward.

Crave Reduction: Preclinical and real-world data show reduced cravings:

- Food & Alcohol
- Nicotine, Cannabis & Cocaine
- Opioids

Mechanisms of GLP-1 in Modulating Craving and Addiction



Ozempic (semaglutide)

- Developed to treat Type 2 diabetes also now widely used for weight loss.
- Lower the risk of heart attack, stroke.
- Lower the risk of worsening kidney problems and heart-related death in adults with Type 2 diabetes and chronic kidney disease (CKD).
- Included in American Diabetes Association (ADA) treatment guidelines, increases insurance coverage since 2018.

How Ozempic (semaglutide) works

- Ozempic (semaglutide) a glucagon-like peptide-1 (GLP-1) agonist.
- It acts like the natural GLP-1 hormone . This hormone helps lower your blood sugar by:
 - making pancreas release more insulin
 - reducing the sugar made by your liver
 - slowing down digestion
- Medication also reduces weight, lower blood pressure, and lowers inflammation which, can help protect both heart and kidneys

Side effects of Ozempic (semaglutide)?

Common Side Effects

- Nausea (16-20%)
- Diarrhea (9%)
- Vomiting (5-9%)
- Stomach pain (6-7%)
- Constipation (3-5%)

Other Side Effects

- Indigestion
- Burping
- Gas
- Acid reflux
- Injection-site reactions
- Fast heart rate
- Tiredness
- Unusual taste in the mouth
- Dizziness

Serious Adverse Events: Need to be monitored for

- **Risk of thyroid tumors**: lump in the neck, trouble breathing or swallowing, hoarseness
- **Vision changes (diabetic retinopathy)**: vision loss, blurred vision, floaters, seeing dark spots
- **Pancreatitis**: stomach or back pain that won't go away
- **Low blood sugar (hypoglycemia)**: shaking, sweating, dizziness, confusion, blurred vision
- **Kidney problems**: changes in urination, swollen feet or ankles, tiredness, nausea
- **Severe stomach problems**: nausea, vomiting, diarrhea, bloating, heartburn
- **Gallbladder problems**: pain in stomach, fever, yellowing eyes, clay-colored stool
- **Serious allergic reaction**: trouble breathing, rash, hives, swollen face, fast heartbeat

What are possible additional Benefits?

- MASH, or metabolic dysfunction–associated steatohepatitis
- Reductions in acute liver failure
- Secondary reductions in some types of heart disease
- May depend on disease stage (e.g., presence of cirrhosis)

GLP-1 Receptor Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: Bridging Hepatic and Cardiovascular Outcomes

<https://onlinelibrary.wiley.com/doi/full/10.1002/cdt3.70048>

What are possible additional Benefits?

- Improved Renal function and CV function (GLP1+ GIP even better)
- Improvement in kidney outcomes: "treatment with tirzepatide (GLP1 + GIP) was associated with significantly lower hazards of all-cause mortality and major adverse cardiovascular and kidney events compared with GLP-1 RA."
- Possible treatment for "craving" based addictions, not just food:
- Gambling
- Substance use disorders (alcohol, tobacco, opioids, cocaine, meth)

Substance Use Reduction: Studies indicate a reduction in cravings for

Reductions in cravings and odds for

opioids (**87%**)

alcohol (**85%**)

cocaine (**75%**)

nicotine (**68%**)

2024 (Wang et al 2024; Martinelli et al 2024)

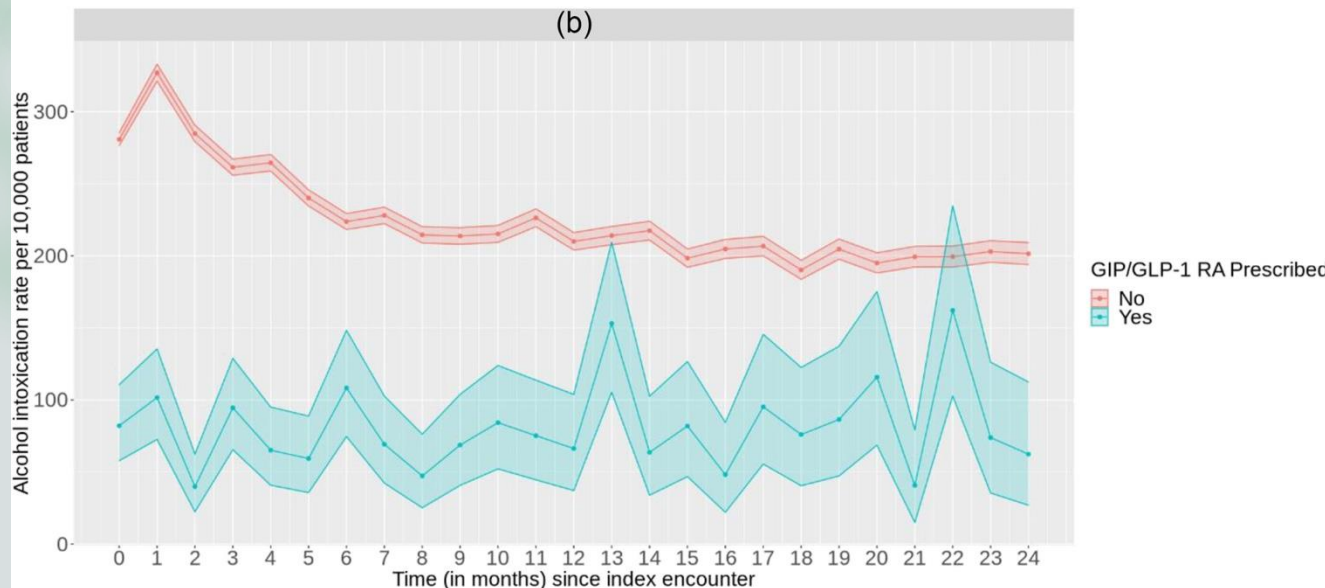
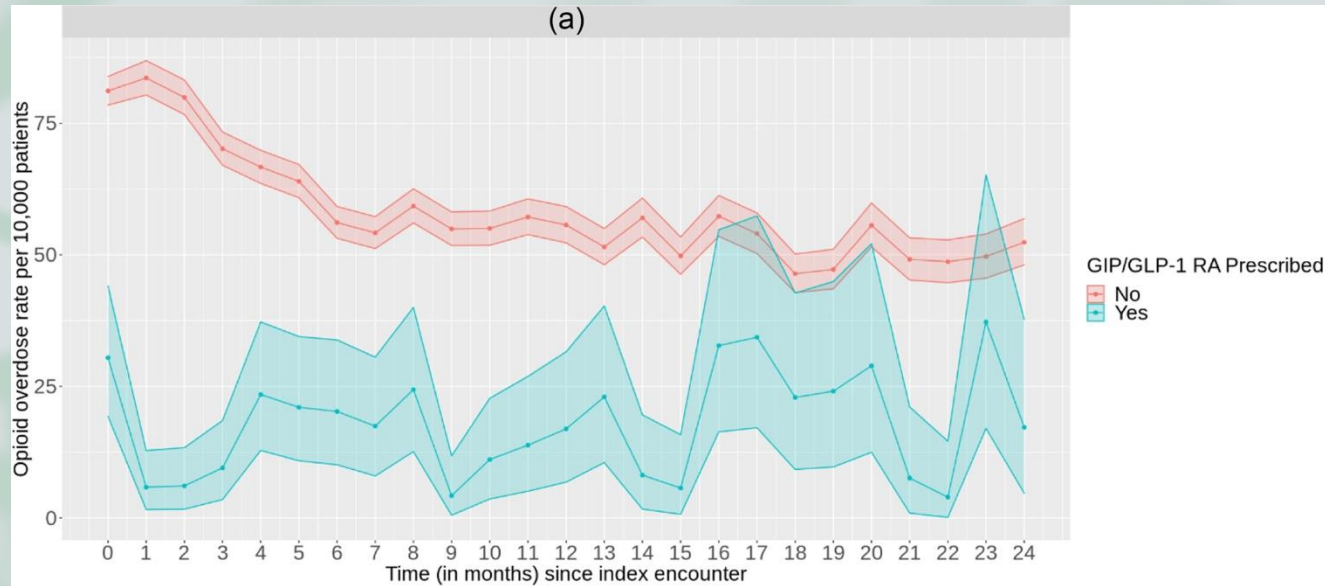
Real-World Data 2024 study of over 500,000 patients showed:

- prescriptions for GIP/GLP-1 RA (specifically Tirzepatide) were associated with lower rates of
 - opioid overdose
 - alcohol intoxication

Real-World Data (Qeadan 2024)

- 1.3 million adult patients (500k+ with OUD, 800k+ with AUD) 2014 to 2022.
- Key Finding: GIP/GLP-1 RA prescriptions were associated with:
 - 40% lower rate of opioid overdose.
 - 50% lower rate of alcohol intoxication
- Comparison: Significant protective effect compared to patients not on these medications
- Limitations: Observational data (cannot prove cause-and-effect); study population limited to those with diabetes/obesity.

OVERDOSE



INTOXICATION

The association between GLP1/GIP prescriptions and substance-related outcomes in patients with opioid and alcohol use disorders: A real-world data analysis (over 500,000 patients)

Addiction, Volume: 120, Issue: 2, Pages: 236-250, First published: 16 October 2024, DOI: (10.1111/add.16679)

- De-identified electronic health record data
- 100 million patients, spanning January 2014 to September 2022
- 503 747 patients with a history of OUD
- 817 309 patients with a history of AUD

Nested Case Control Study (Abegaz 2026)

- Does GLP-1 reduce the odds of new diagnosis of substance use disorder among adults with diabetes or obesity?
 - 22,652 participants – 74% reduction in alcohol use disorder
 - 13,226 in the OUD – 69% reduction in opioid use disorder
 - 42,320 in the NUD – 68% reduction in nicotine use disorder
 - 9,296 in the CUD – 75% reduction in cocaine use disorder

Outcome from very large retrospective study (Cai 2026)

- Does GLP-1 reduce incidence of SUD outcomes among Veterans treated for diabetes?
 - This study of 1.3 million patients with opioid use disorder or AUD reported those who were started on a GLP-1RA had:
 - 50% Reduction in SUD-related Mortality
 - 39% Reduction in Drug Overdose
 - 31% Reduction in SUD-related ER Visits
 - 25% Reduction in Suicidal Ideation or Attempts
- compared to veterans on another diabetes medication

GLP-1 RA use was associated reduced risks of harmful outcomes from

- 18% reduction in outcomes due to alcohol abuse
- 25% reduction in outcomes due to opioid abuse
- 20% reduction in outcomes due to nicotine abuse
- 20% reduction in outcomes due to cocaine abuse
- 14% reduction in outcomes due to cannabis abuse

- 14% lower odds of any SUD compared with non-users

Limitations of study

- Study population was limited to those with **diabetes or obesity**
- It's **observational nature** precludes causal inference
- Although prescription start dates and diagnosis dates were identified the **temporal relationship** between GLP-1 RA initiation and the onset of SUDs may not be precise
- Medication exposure was inferred from prescription records and may not reflect actual **adherence**.

GLP-1 and GIP combination drugs

TAB Study ongoing now

The Tirzepatide as an Adjunct to Buprenorphine (TAB) Trial

- 31-week, multi-site study (completion July 2027)
- Evaluating tirzepatide (a GLP-1 and GIP combination drug)

Study Question:

Does tirzepatide improves retention and reduces illicit opioid use in patients with moderate to severe opioid use disorder (OUD)

Funded by the NIH

Possible future study comparing efficacy of GLP-1 VS GLP-1 + GIP

- Not Placebo controlled but head-to-head comparison
- Everybody gets the benefit of treatment
- Study Questions:
 - Which is most affordable per effective treatment
 - Which has fewer side effects
 - Which has fewer adverse events

BOTTOM LINE

These findings suggest that agents designed to improve glycemic control and cause weight loss (semaglutide and tirzepatide) also have significant neurobiological effects that may help manage addictive behaviors.

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