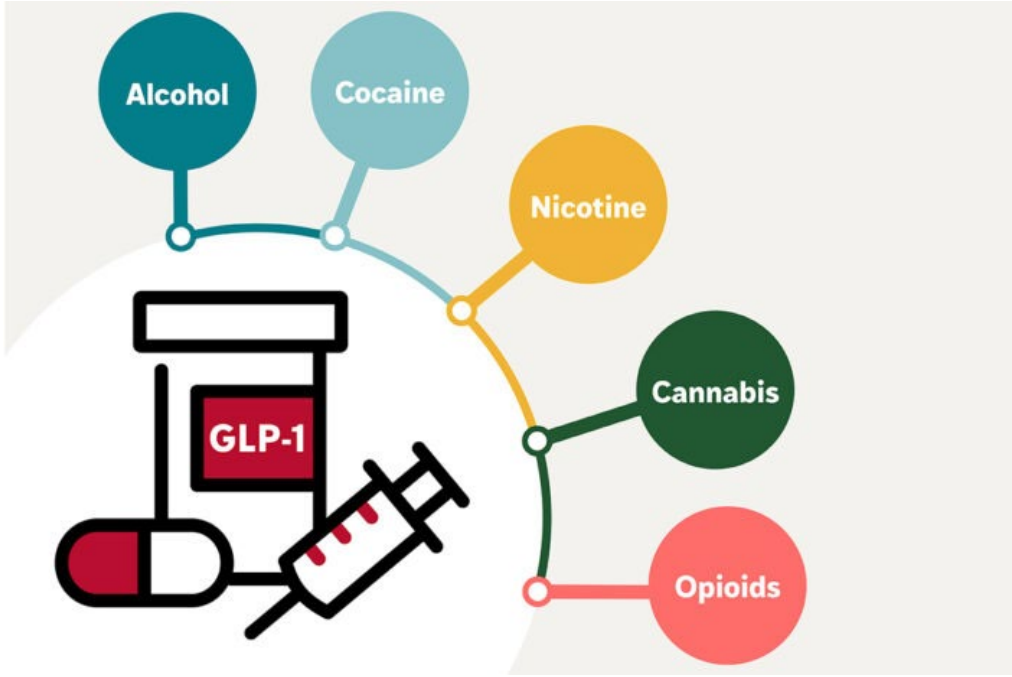
Rewiring Reward: GLP-1 Receptor Agonists in Substance Use Disorders



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Disclaimer

Annie Saefong has no relevant financial relationship(s) with ineligible companies to disclose.

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Learning Objectives

1	Explain the mechanism of action (MOA) of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in substance use disorders (SUDs).
2	Recognize the potential for GLP-1RAs in SUDs by evaluating current evidence.

Background

46.3 million people age 12 or older in the U.S. had a SUD (2021)

Impact

- Morbidity: 110,000 deaths from drug overdoses (2022)
- Healthcare costs: $120 billion annually
- Health Outcomes: Increased risk for developing chronic illnesses
- Social: Increased rates of unemployment and increased community crime rates

National Institute on Drug Abuse. “NIDA IC Fact Sheet 2025 | National Institute on Drug Abuse.” *National Institute on Drug Abuse*, 7 Mar. 2024, nida.nih.gov/about-nida/legislative-activities/budget-information/fiscal-year-2025-budget-information-congressional-justification-national-institute-drug-abuse/ic-fact-sheet-2025.

Check-in Question:

Which of these medications are **not** FDA-approved in SUDs?

A. Naltrexone

B. Varenicline

C. Methadone

D. Semaglutide

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FDA-Approved Treatment Options

Alcohol Use Disorder

- Naltrexone
- Acamprosate
- Disulfiram

Nicotine Use Disorder/Smoking Cessation

- Nicotine replacement
- Varenicline
- Bupropion SR

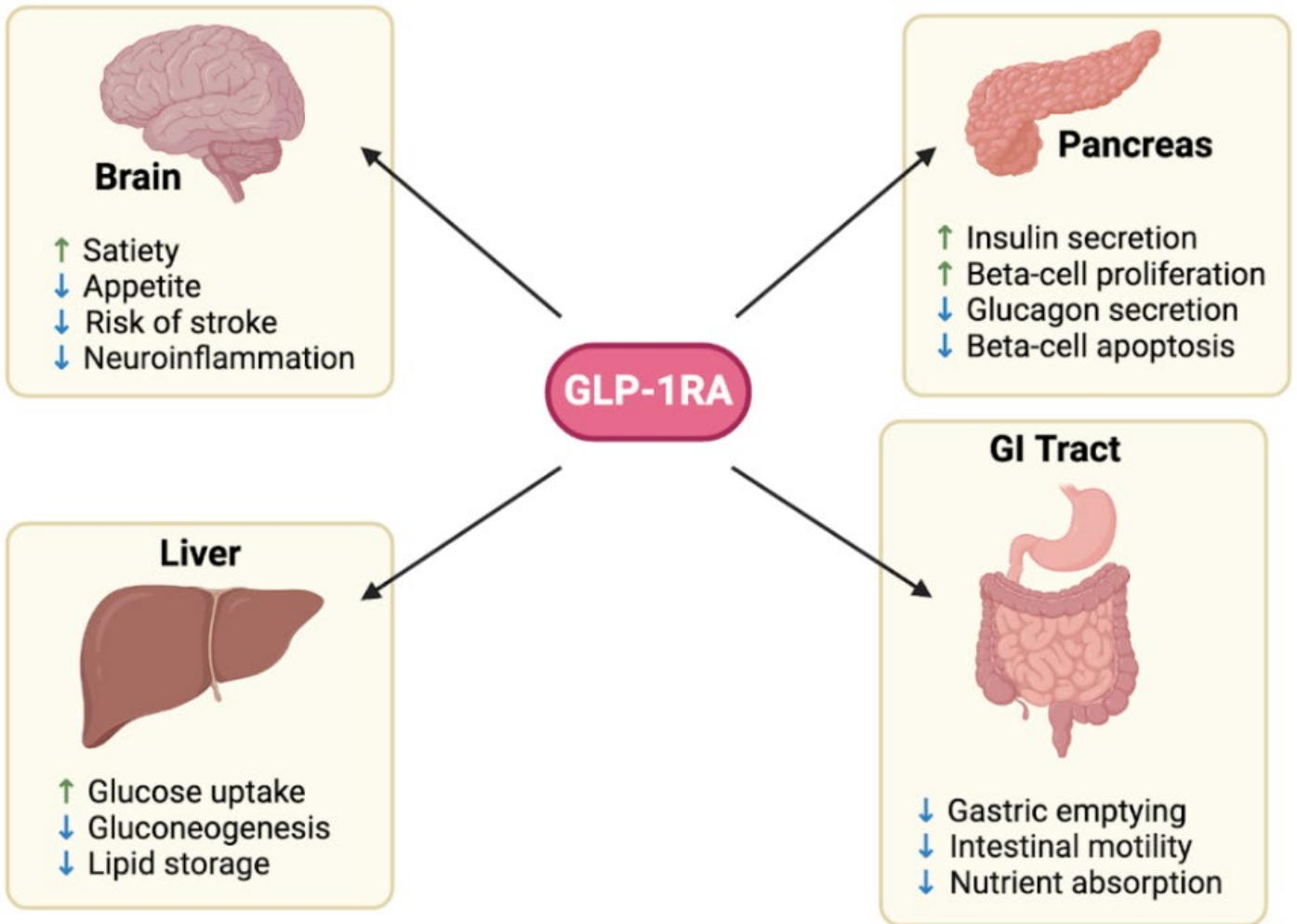
Opioid Use Disorder

- Buprenorphine
- Methadone

Stimulant Use Disorder

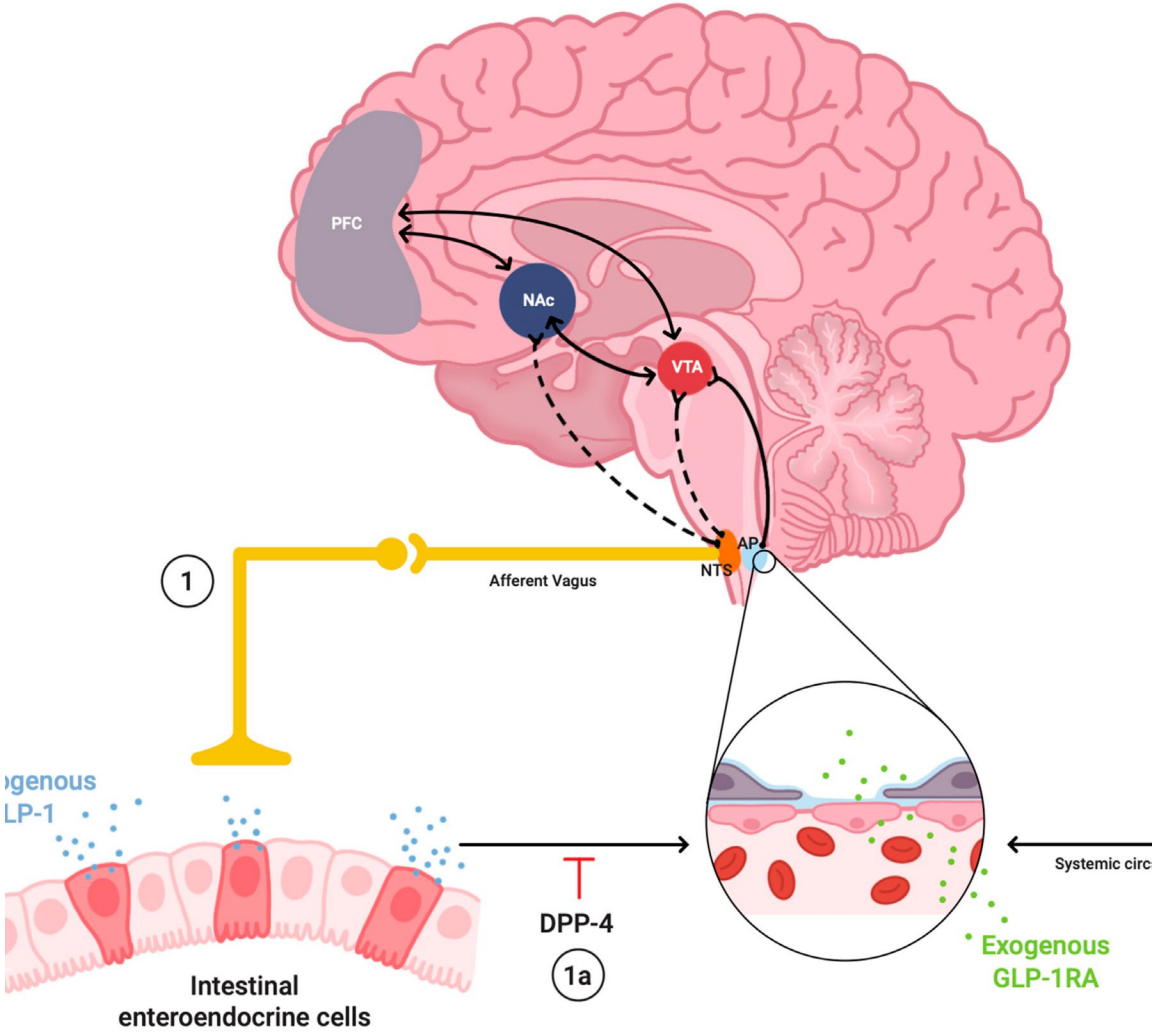
- No FDA-approved medications

GLP-1RA Mechanisms of Action



University of North Carolina at Chapel Hill. https://medrac.web.unc.edu/2025/03/glp-1-receptor-agonists/

GLP-1RAs MOA in SUDs



The reward pathway

- Stimuli → Dopamine (DA) → Mesolimbic Reward Pathway → Pleasure and motivation → Reinforcement → Habit formation
- Mesolimbic reward pathway
  - Ventral Tegmental Area (VTA)
  - Nucleus accumbens (NAc)
  - Prefrontal cortex (PFC)
  - Nucleus tractus solitarius (NTS)

GLP-1RAs modulate dopamine reward-related pathway to reduce cravings and substance-seeking behaviors

Amorim Moreira Alves G, Teranishi M, Teixeira de Castro Gonçalves Ortega AC, James F, Perera Molligoda Arachchige AS. Mechanisms of GLP-1 in Modulating Craving and Addiction: Neurobiological and Translational Insights. *Medical Sciences*. 2025; 13(3):136. https://doi.org/10.3390/medsci13030136

Check-in Question:
How can GLP-1 RAs help in SUDs?

A. Modulate norepinephrine pathways to increase appetite

B. Inhibit dopamine release to increase cravings and substance-seeking behaviors

C. Modulate dopamine reward-related pathways to reduce cravings and substance-seeking behaviors

D. Stimulate insulin secretion in the pancreas

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D. Stimulate insulin secretion in the pancreas

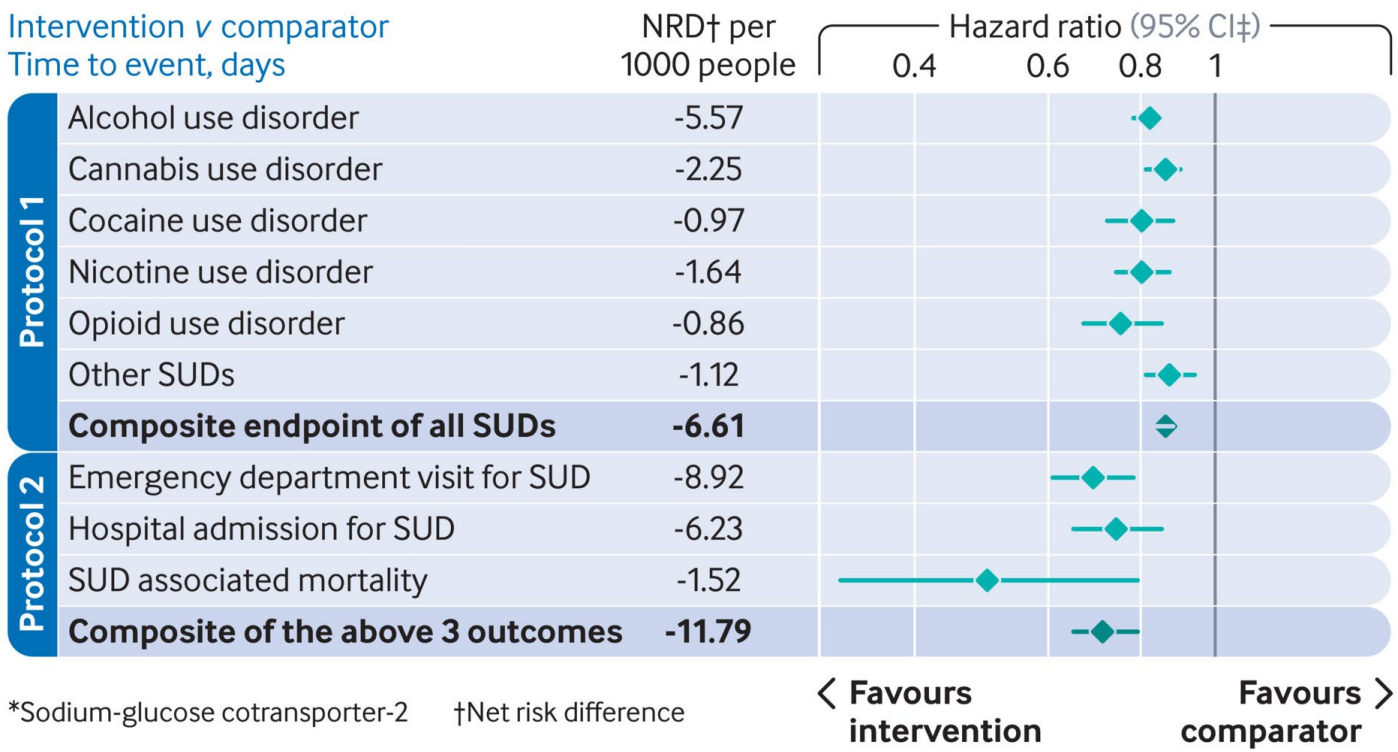
CLINICAL STUDIES

Title	GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND RISK OF SUBSTANCE USE DISORDERS AMONG US VETERANS WITH TYPE 2 DIABETES: COHORT STUDY
Objective	To investigate whether initiation of GLP-1RAs is associated with both reduced risks of incident alcohol, cannabis, cocaine, nicotine, opioid, and other SUDs in people with no history of SUDs (protocol 1) and with reduced risk of SUD related adverse clinical outcomes among people with a pre-existing SUD (protocol 2)
Background	Total: 606,434 US Veterans with type 2 diabetes, followed for 3 years Cohort study at VA Saint Louis Health Care System

Methods	Protocol 1: GLP-1 RA (n=124,001) or SGLT-2i (n=400,816)
	• 7 trials of separate SUDs
	Protocol 2: GLP-1 RA (n=16,768) and SGLT-2i (n=64,849)
	• 1 trial of pre-existing SUD and adverse SUD related clinical events
	
	• Medications:
	  • GLP-1RA: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and tirzepatide
	  • SGLT-2i: bexagliflozin, canagliflozin, dapagliflozin, ertugliflozin, sotagliflozin

Cai M, Choi T, Xie Y, Al-Aly Z. Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes: cohort study. BMJ. 2026;392:e086886. doi:https://doi.org/10.1136/bmj-2025-086886

Results



Cai M, Choi T, Xie Y, Al-Aly Z. Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes: cohort study. BMJ. 2026;392:e086886. doi:https://doi.org/10.1136/bmj-2025-086886

Ongoing Clinical Trials

Trial Name	Objectives/Goals	Recruitment Status	Study Completion	Identifier
Cessation or Reduction of Alcohol Consumption in Veterans: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of a GLP-1 Receptor Agonist Semaglutide in U.S. Veterans With Alcohol Use Disorder (CRAVE)	Semaglutide and mod-severe AUD in Veterans over 28 weeks	Not Yet Recruiting	05-26-2029	NCT07218354
GLP-1R Agonist Treatment for Opioid Use Disorder	Semaglutide and opioid use disorder for 12 weeks	Recruiting	11-2026	NCT06548490
Effect of Glucagon-like Peptide-1 (GLP-1) Receptor Agonist Stimulation on Smoking Consumption in Type 2 Diabetes Patients	GLP-1RA and nicotine use in patients with T2DM	Enrolling by invitation	07-01-2026	NCT06924697
Semaglutide Therapy for Alcohol Reduction (STAR)	Semaglutide safety and may reduce alcohol drinking in people with AUD	Recruiting	12-31-2030	NCT06015893
GLP-1 Receptor Agonists to Decrease Ethanol and CVD Risk in HIV (GL1DER HIV RCT)	Semaglutide with alcohol and tobacco reduction	Not Yet Recruiting	07-31-2030	NCT07221214

Check-in Question (True or False):

Alcohol use disorder has the largest amount of published clinical evidence supporting the use of GLP-1RAs.

A. True

B. False

Check-in Question (True or False):

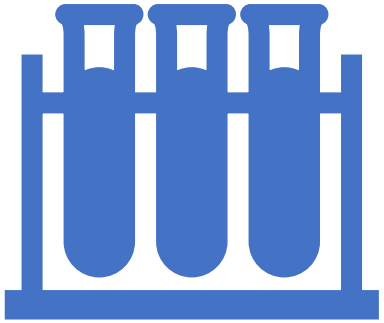
Alcohol use disorder has the largest amount of published clinical evidence supporting the use of GLP-1RAs.

A. True

B. False

Key takeaways

1. GLP-1RAs act in metabolic and brain reward circuits to reduce intake in SUDs.



2. Current evidence highlights the potential of GLP-1RAs in treatment of SUDs, however, data is limited and further studies are needed.

Thank you!

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