

GLP-1 Receptor Agonists and Incident Substance Use Disorders in Adults With Obesity and Without Diabetes

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SUD: ≥2 of 11 DSM-5 Criteria Within 12 Months

Impaired control	Social impairment	Risky use	Pharmacologic
4 criteria	**3** criteria	**2** criteria	**2** criteria
More or longer than intended, can’t cut down, time spent, craving	Role failure, social problems, activities given up	Hazardous use, use despite harm	Tolerance, withdrawal

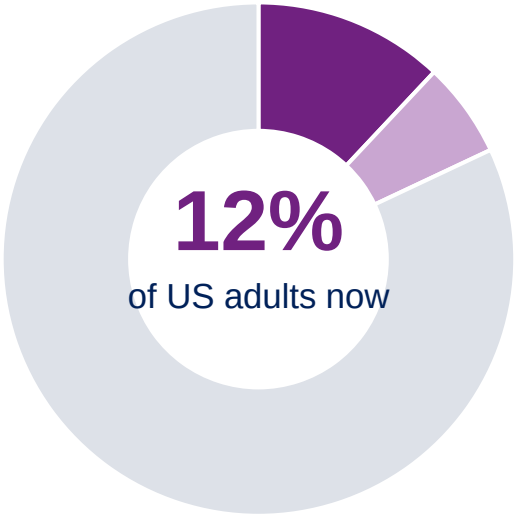
Severity

Mild 2–3 criteria → **Moderate** 4–5 criteria → **Severe** ≥6 criteria

APA, DSM-5-TR (2022). Tolerance and withdrawal are not counted with appropriately supervised medical use. Study outcome: any ICD-10-CM F10–F19 code (includes nicotine and unspecified-use codes).

GLP-1 Use and SUDs Are Both Common

GLP-1 drug use is widespread

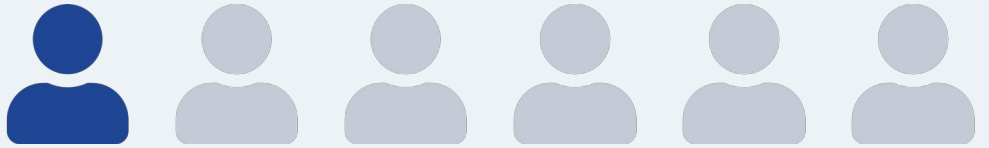


- **12%** currently taking one
- **About 6%** took one previously
- **82%** never taken one

23% of adults with a recent overweight or obesity diagnosis currently take one

SUDs are common and undertreated

44.6M people aged 12+ had a past-year SUD (15.3%)

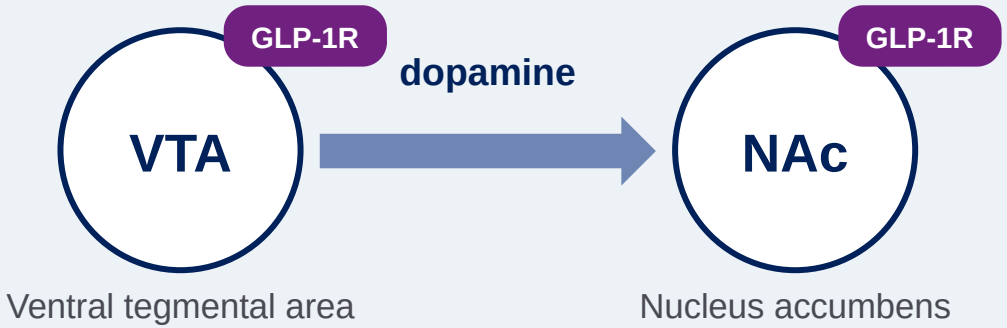


Only 1 in 6 who needed treatment received it

KFF Health Tracking Poll, Oct 27–Nov 2, 2025 (n = 1,350); "about 6%" = 18% ever minus 12% current. SAMHSA, 2025 National Survey on Drug Use and Health.

Reward-Pathway Biology and Early Human Signals

Mechanism (preclinical)



1. GLP-1 receptors sit in reward circuitry
2. GLP-1 RAs blunt drug-induced dopamine signaling
3. Rodents self-administer less alcohol, nicotine, cocaine, opioids

Human evidence

Randomized trial, 2025 · Hendershot, JAMA Psychiatry

Semaglutide in 48 adults with alcohol use disorder: lower laboratory alcohol intake, drinks per drinking day, and craving

Target trial emulation, 2026 · Cai, BMJ

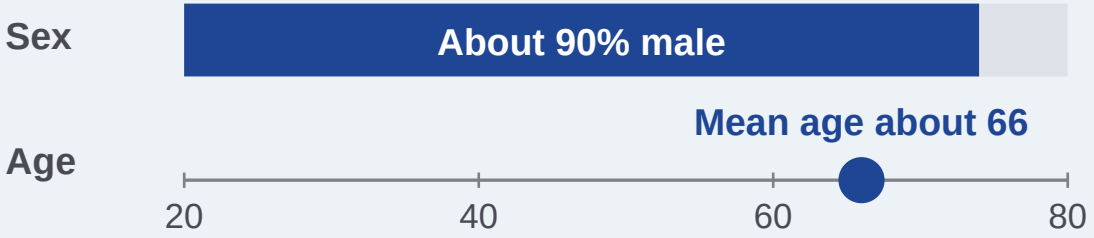
524,817 veterans with type 2 diabetes: GLP-1 RA vs SGLT2 inhibitor, composite SUD HR 0.86 (95% CI 0.83–0.88)

VTA, ventral tegmental area; NAc, nucleus accumbens; GLP-1R, GLP-1 receptor. Preclinical evidence: Jerlhag, Front Pharmacol 2023. Additional studies on backup slide.

Prior Evidence: Mostly Older Men With Diabetes

Veteran cohort (Cai et al., BMJ 2026)

US veterans with type 2 diabetes

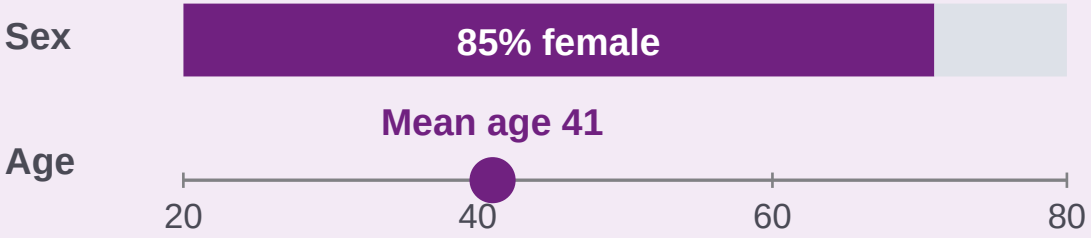


SGLT2 inhibitors (diabetes medication)

Veterans Affairs health system

This study

Adults with obesity, without diabetes



Phentermine or orlistat (obesity medications)

67 US healthcare organizations

Our question: in adults with obesity and no diabetes, is GLP-1 RA vs phentermine or orlistat associated with incident SUD at 1 and 2 years?

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Design: GLP-1 RA vs Phentermine or Orlistat

Data source

TriNetX US Collaborative Network

67 US healthcare organizations

Eligibility

Ages 18–70; obesity diagnosis ≤1 year before first prescription

Excluded: diabetes, SUD in prior 2 years, bariatric surgery

GLP-1 RA

Semaglutide, liraglutide, tirzepatide

n = 384,595

Comparator

Phentermine or orlistat

n = 181,354

1:1 propensity score matching

179,207

per group

Primary outcome

Any new ICD-10 F10–F19 diagnosis at 1 and 2 years

Secondary outcomes

10 substance-specific SUDs, drug poisoning, suicidal ideation, death, MI, stroke, pancreatitis

Analysis

Cox hazard ratios (95% CI); E-values for unmeasured confounding

About 114.7 million patients; data as of March 5, 2026. GLP-1 RA includes tirzepatide (dual GIP/GLP-1 RA). Naltrexone, bupropion, topiramate avoided as comparators (known effects on substance use).

Matched Groups Were Well Balanced

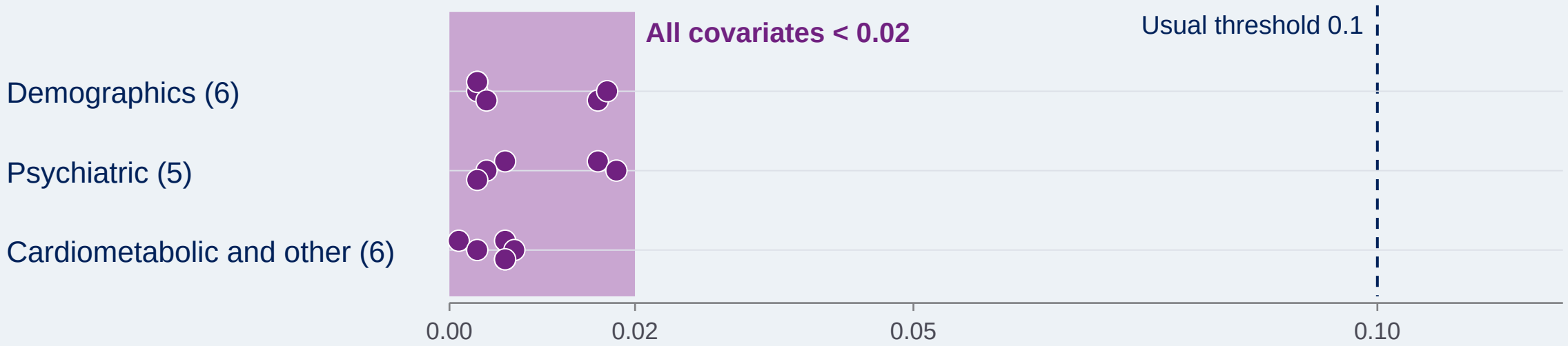
179,207
patients per group

85%
female

41 years
mean age

19
covariates matched

Standardized mean difference (SMD) after matching



Shown: 17 covariates reported in Table 1 (age, sex, race, ethnicity, comorbidities). Also matched: phobic anxiety, acute and unspecified kidney failure, sleep apnea. Diagnoses matched as present or absent.

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21% Lower Hazard of Incident SUD at 1 and 2 Years

1 year

HR 0.79

95% CI 0.74–0.83



2,253 vs 3,238 patients with events

2 years

HR 0.79

95% CI 0.76–0.83



3,294 vs 5,178 patients with events

E-value 1.85: an unmeasured confounder would need a risk ratio ≥1.85 with both treatment and SUD to explain this away

Follow-up time differed between groups; compare hazards, not raw counts. Nicotine diagnoses made up most composite events (2,097 vs 3,561 at 2 years). Log-rank P<0.001 at both time points.

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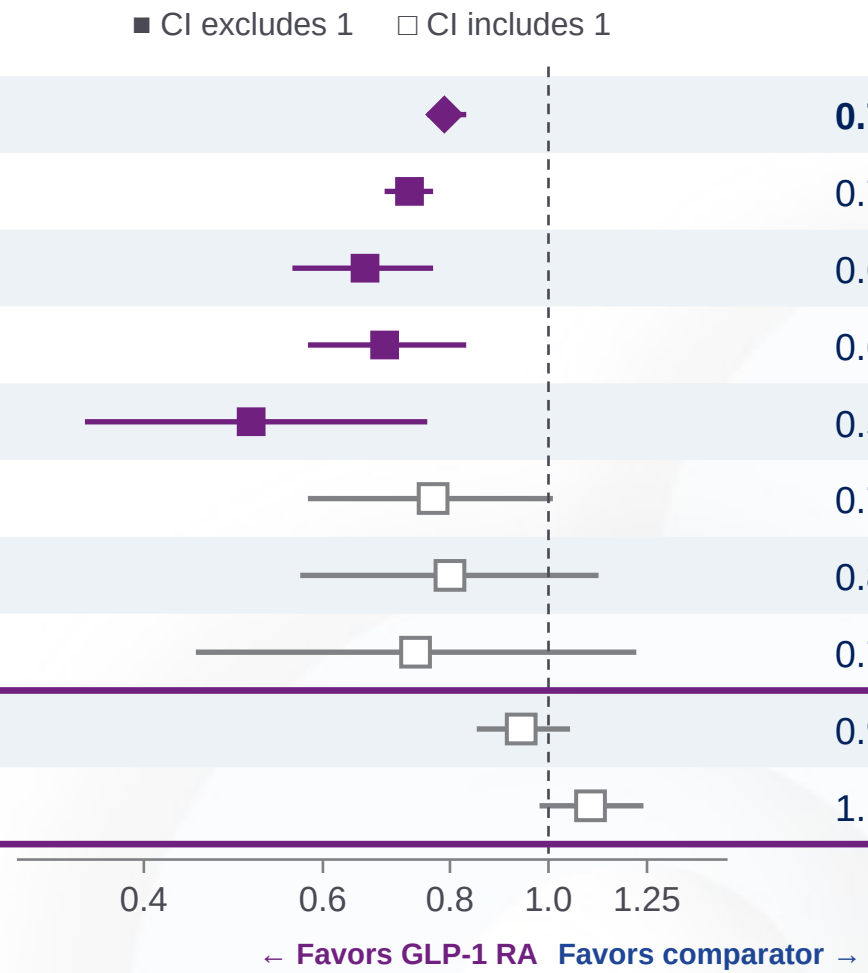
Lower Hazards for Nicotine, Opioid, Cocaine

Outcome (ICD-10)	GLP-1 RA / comparator	HR (95% CI)
Composite SUD (F10–F19)	**3,294 / 5,178**	**0.79 (0.76–0.83)**
Nicotine (F17)	2,097 / 3,561	0.73 (0.69–0.77)
Opioid (F11)	234 / 452	0.66 (0.56–0.77)
Other or multiple (F19)	193 / 347	0.69 (0.58–0.83)
Cocaine (F14)	37 / 89	0.51 (0.35–0.76)
Other stimulant (F15)	83 / 135	0.77 (0.58–1.01)
Sedative or hypnotic (F13)	56 / 88	0.80 (0.57–1.12)
Inhalant (F18)	25 / 42	0.74 (0.45–1.22)
Alcohol (F10)	656 / 876	0.94 (0.85–1.05)
Cannabis (F12)	534 / 604	1.10 (0.98–1.24)



Events: GLP-1 RA / comparator. Hallucinogen (F16) suppressed (<10 events). HRs from Cox models; secondary outcomes not adjusted for multiplicity.

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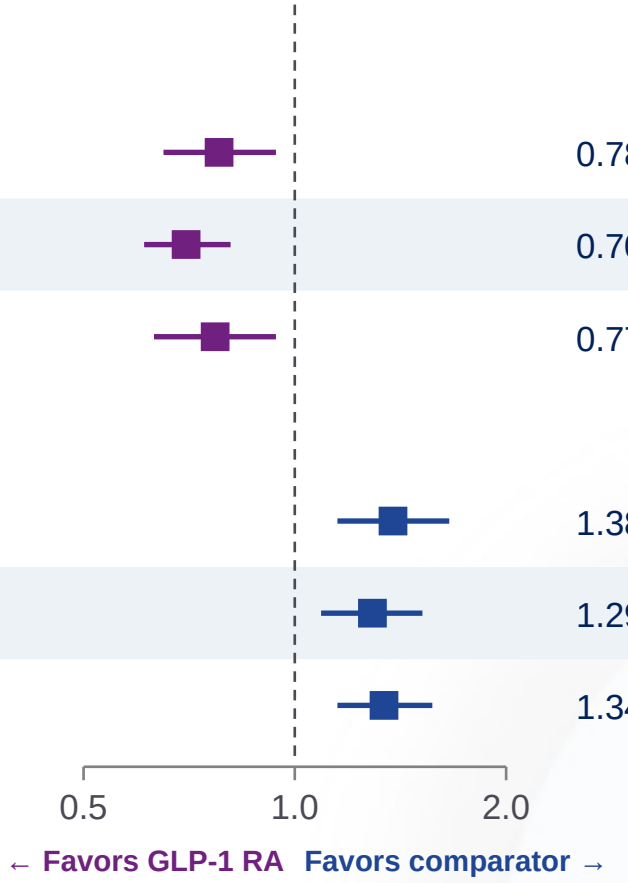
Cardiovascular Signals Suggest Residual Confounding

Outcome (ICD-10)	GLP-1 RA / comp.	HR (95% CI)
Substance-related and overall		
Drug poisoning	182 / 293	0.78 (0.65–0.94)
Suicidal ideation	288 / 517	0.70 (0.61–0.81)
All-cause mortality	151 / 254	0.77 (0.63–0.94)
Cardiovascular and pancreatic		
Myocardial infarction	232 / 215	1.38 (1.15–1.66)
Ischemic stroke	292 / 288	1.29 (1.09–1.52)
Acute pancreatitis	315 / 298	1.34 (1.15–1.57)



Interpreting these signals

- Phentermine is contraindicated in CVD: comparators likely lower risk
- More cardiometabolic disease in the GLP-1 RA group before matching; severity not matched
- SELECT (RCT, different population): semaglutide lowered major CV events
- Pancreatitis is a labeled GLP-1 RA warning
- Favorable results, including mortality, share this risk

Two-year results. Ischemic stroke = ICD-10 I63. SELECT: Lincoff et al., N Engl J Med 2023. Secondary outcomes exploratory.

Bias Could Push Estimates Either Way

Toward the null: could hide a benefit

- Phentermine label contraindication ("history of drug abuse") may steer higher-risk patients to GLP-1 RAs
- GLP-1 drugs obtained outside the network
- Stopping or switching after the first prescription

Away from the null: could exaggerate a benefit

- Greater access and engagement among GLP-1 RA initiators
- Phentermine misuse could be coded as stimulant use disorder

Not matched

Severity, BMI, smoking, index year

Not captured

Socioeconomic status, dose, adherence

Outcome capture

Codes miss many SUDs

Generalizability

85% female; ages 18–70

E-value for the primary outcome: 1.85. No adjustment for multiple comparisons.

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Screen for Substance Use in Obesity Care

1 Screen

- USPSTF: screen adults for unhealthy alcohol and drug use; ask all adults about tobacco
- Brief tools: AUDIT-C or TAPS

94.5% of adults with untreated SUD did not seek or think they needed it

2 Tailor

- Phentermine label: contraindicated with "history of drug abuse"
- Monitor for alcohol use disorder after bariatric surgery

3 Discuss

- GLP-1 effects on substance use: an area of research, not an established benefit
- Treat or refer SUD with evidence-based care

USPSTF: JAMA 2018;320:1899 (alcohol); 2020;323:2301 (drugs); 2021;325:265 (tobacco). SAMHSA NSDUH 2025. King et al., JAMA 2012 (bariatric). Phentermine prescribing information.

Lower SUD Hazard Observed; Trials Needed

- **21% lower hazard** of incident SUD over 2 years (358,414 adults with obesity, no diabetes)
- **Most consistent** for nicotine and opioid use disorders; cocaine estimate imprecise
- **Associations, not causal effects;** residual confounding likely
- **Next:** randomized trials, and SUD screening in obesity care now





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