# GLP-1 Treatment Associated with a 39% Lower Risk of Repeat Substance Overdose

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Last updated July 9, 2026 • Check for updates at EpicResearch.org

## Key Findings:

- Among adults who have had a documented substance overdose, those who started on a GLP-1 had a 39% lower risk of a repeat overdose within three years of their overdose compared to patients who were never prescribed a GLP-1. Patients who started and later discontinued a GLP-1 still had a 20% lower risk than patients who never used a GLP-1.
- The protective association was consistent across initial overdose type. Patients whose first overdose involved alcohol had a 40% lower risk during active GLP-1 use, and patients whose first overdose did not involve alcohol had a 37% lower risk.
- When patients on medications for opioid, alcohol, or nicotine use disorder were excluded from the analysis, the association strengthened to a 44% lower risk during active GLP-1 use.

Adults who survive an overdose of opioids, alcohol, or other substances face substantially elevated risk of a subsequent overdose. Prior studies report that 15% or more of survivors experience a repeat overdose within a year, with the highest risk concentrated in the weeks immediately following the index event.[1,2] Effective post-overdose interventions remain limited: medications for opioid use disorder reduce repeat overdose risk substantially but reach only a small minority of survivors, and no widely used pharmacotherapy addresses the broader range of substances involved in overdose events.[3] Glucagon-like peptide-1 (GLP-1) receptor agonists, a class of medications originally approved for type 2 diabetes and later for obesity, have drawn growing interest as potential treatments for substance use disorders. GLP-1s are expressed in brain regions that govern motivation and reward. Preclinical and clinical studies have shown that GLP-1s reduce alcohol intake, blunt the pleasurable effects of opioids and stimulants, and might reduce cravings across multiple substance classes.[4,5] A recent large cohort study of U.S. veterans with type 2 diabetes and a pre-existing substance use disorder found that GLP-1 initiation was associated with roughly 40% lower risk of overdose compared to other diabetes medications.[6] Whether this signal extends to patients who have already experienced an overdose, regardless of their original indication for GLP-1 therapy, has not been established.

We studied 683,800 U.S. adults with an emergency department or inpatient overdose encounter that occurred between January 1, 2017, and March 9, 2026. Patients who had already been prescribed a GLP-1 before their overdose were excluded so that all GLP-1 exposure occurred after the overdose event. We accounted for demographics, social vulnerability and rurality based on latest address, BMI category, diabetes, mental health diagnoses, and medications for opioid, alcohol, or nicotine use disorder. To assess robustness, we repeated the analysis for three subgroups: patients whose first overdose involved alcohol, patients whose first overdose did not involve alcohol, and patients not receiving any addiction-treatment medications.

Active GLP-1 use after an overdose was associated with a 39% lower risk of a repeat overdose between 30 days and three years after the overdose event, compared to patients who were never prescribed a GLP-1, as seen in Figure 1. Patients who started a GLP-1 and later discontinued it still had a 20% lower risk than patients who never used a GLP-1, suggesting that the association with lower overdose risk might extend beyond the period of active treatment. The pattern was consistent across initial overdose type:

patients whose first overdose involved alcohol had a 40% lower risk during active GLP-1 use, while those whose first overdose did not involve alcohol had a 37% lower risk. Patients who discontinued a GLP-1 retained a similar protective association in both subgroups (18% lower risk for alcohol, 24% lower risk for non-alcohol). The association was still present when patients on medications for opioid, alcohol, or nicotine use disorder were excluded, with a 44% lower risk during active GLP-1 use and a 28% lower risk after discontinuation. This suggests the finding is not explained by the addiction-treatment medications some patients were already taking.

## Risk of Repeat Overdose by GLP-1 Status

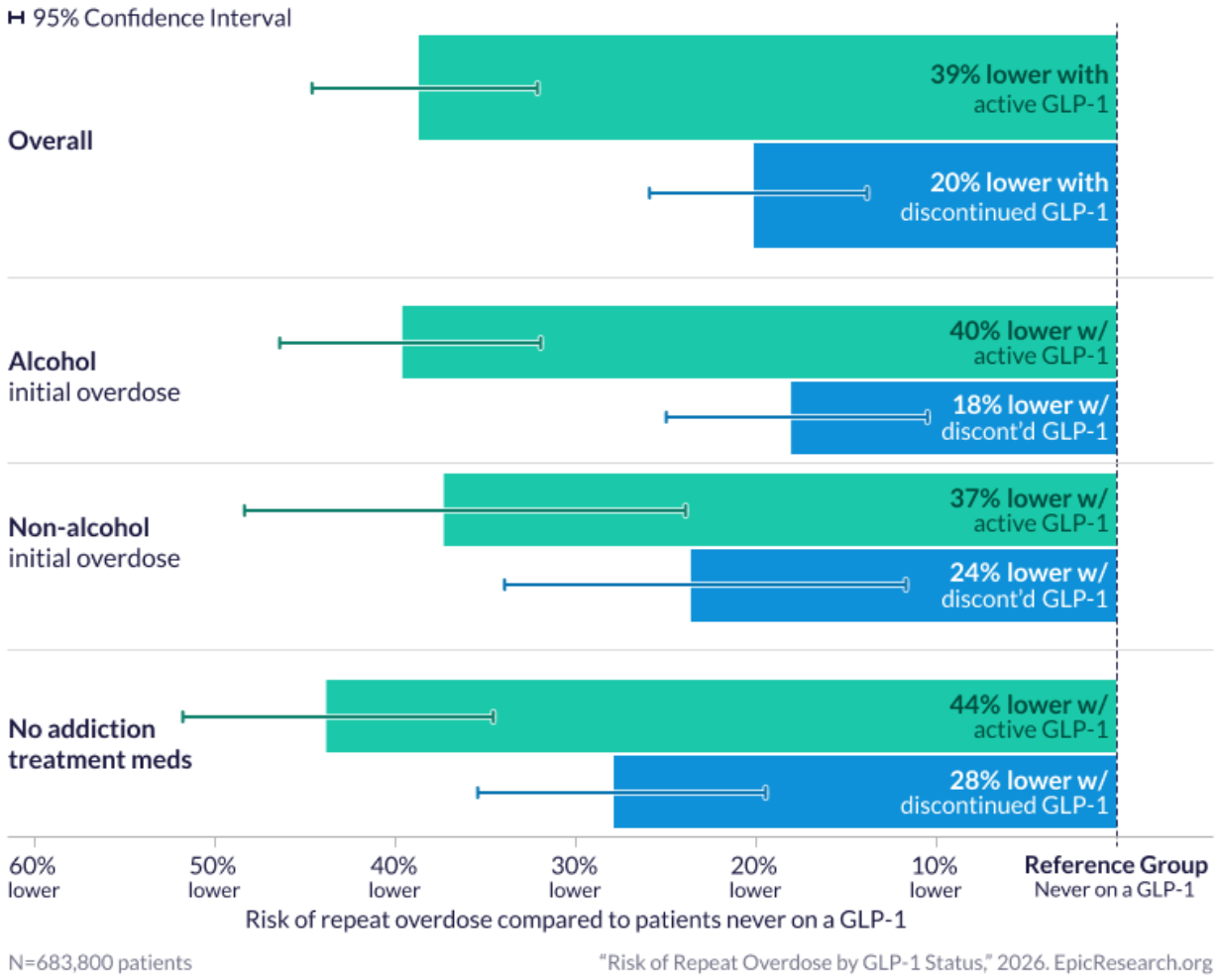


*Figure 1. Risk of repeat overdose within three years among patients with active GLP-1 use and patients who started and later discontinued a GLP-1, compared to patients never prescribed a GLP-1, across the overall group and three sensitivity analyses (alcohol initial overdose, non-alcohol initial overdose, and patients not on addiction-treatment medications).*

Patients who start GLP-1s after an overdose differ in important ways from those who do not; they might have more consistent engagement with their healthcare team, better access to care, or other unmeasured differences we could not capture. Some or all of the lower repeat-overdose risk could reflect those kinds of differences rather than the medication itself.

*These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 307 million patient records from 2,000 hospitals and more than 49,000 clinics from all 50 U.S. states, Canada,*

*Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientist. The two teams came to similar conclusions. Graphics by Brian Olson.*

## References


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## Data Definitions

| Term | Definition |
|---|---|
| Study period | 1/1/2017 to 3/9/2026 |
| Study population: inclusion | Patients with:<br>• A first **overdose** encounter (ED or inpatient) on or after January 1, 2017<br>• Most recent address in the U.S.<br>• A BMI of 25 or higher around the **index date**<br>• Prior engagement (one or more outpatient encounters more than one year prior to index overdose AND one or more outpatient encounters after index overdose) |
| Study population: exclusion | Patients with:<br>• An assault-related overdose (ICD-10-CM code T* with 7th character = 3)<br>• A **GLP-1** order prior to their first **overdose** encounter<br>• A methadone overdose (ICD-10-CM code T40.3X*) diagnosis |
| Index date | First qualifying **overdose** encounter (ED or inpatient) which must occur within the **study period**. |
| Exposure | **GLP-1** initiation after the index **overdose** encounter, modeled as a time-varying covariate (active use vs. discontinued vs. never) |
| Outcome | Subsequent ED or inpatient encounter for an **overdose** between 30 days and three years after the **index date** |
| Censoring | Subsequent overdose encounter (outcome), death, or last encounter date |
| Overdose | ICD-10-CM code T* restricted to 7th character = 1 (accidental), 2 (intentional self-harm), or 4 (undetermined)<br>Opioid: a billing or diagnosis with ICD-10-CM code F11.12*, F11.22*, F11.92*; T40.1X* (heroin), T40.2X* (opioid), T40.41* (fentanyl), T40.60* (opiate) |

| | |
|---|---|
| | Alcohol: a billing or encounter diagnosis with ICD-10-CM code F10.12*, F10.22*, F10.92*, T51.0X*<br>Stimulants: a billing or encounter diagnosis with ICD-10-CM code T43.62* or F15.[129]2*<br>Sedative/hypnotics: a billing or encounter diagnosis with ICD-10-CM code T42.3X*, T42.4X*, or F13.[129]2*<br>Cannabinoid: a billing or encounter diagnosis with ICD-10-CM code T40.71*, T40.72*, F12.[129]2*<br>Cocaine: a billing or encounter diagnosis with ICD-10-CM code T40.5X* or F14.[129]2*<br>Hallucinogens: a billing or encounter diagnosis with ICD-10-CM code T40.8X*, T40.99*, or F16.[129]2* |
| GLP-1 | An outpatient prescription or historical medication for a glucagon-like peptide-1 receptor agonist (e.g., semaglutide, liraglutide, dulaglutide, tirzepatide, exenatide) |
| Confounders | Evaluated sex<br>Age group: 18–34, 35–49, 50–64, 65–74, 75+<br>**Race and ethnicity**: non-exclusive flags for Black or African American and Hispanic or Latino<br>Social Vulnerability Index quintile<br>RUCA (rural-urban commuting area)<br>BMI classification<br>Type 2 diabetes: any diagnosis with ICD-10-CM code E11*<br>Mental health diagnoses (any prior to censor): anxiety (ICD-10-CM code F40*, F41*, F06.4*, F93.0*, F94.0*); depression (ICD-10-CM code F32*, F33*, F06.31*, F06.32*, F34.1*); ADD/ADHD (ICD-10-CM code F90*); bipolar (ICD-10-CM code F31*); psychotic disorders (ICD-10-CM code F20*, F21*, F22*, F23*, F24*, F25*, F28*, F29*); PTSD (ICD-10-CM code F43.1*)<br>Medication for opioid use disorder (MOUD): ATC code N07BC*<br>Medication for alcohol use disorder (MAUD): ATC code N07BB*<br>Medication for nicotine dependence (MNUD): ATC code N07BA* |
| Sensitivity analyses | Alcohol initial **overdose** only<br>Non-alcohol initial **overdose** only<br>Patients with no **MOUD**, **MAUD**, or **MNUD** |
| Model specifications | Cox proportional hazards with GLP-1 exposure (active use, discontinued, never) as a time-varying covariate |
| Limitations | Confounding by indication: patients who initiate GLP-1s may be more engaged in healthcare, have different health-seeking behaviors, or differ systematically on unmeasured factors compared with patients who do not.<br>GLP-1 documentation in Cosmos may not capture all prescribing, particularly prescriptions filled outside contributing health systems.<br>Time-varying confounding may not be fully addressed by the Cox PH approach.<br>Generalizability is limited to patients in health systems contributing to Cosmos. |

## Table 1. Population Characteristics

| Category | Value | Total | Total (%) | GLP Discontinued (%) | GLP Started (%) | No GLP (%) |
|---|---|---|---|---|---|---|
| All | All | 683,800 | 100.0% | 2.5% | 0.7% | 96.8% |
| Repeat OD | 1 | 156,110 | 22.8% | 3.9% | 7.9% | 23.4% |
| Reliable Sex | Female | 288,382 | 42.2% | 57.7% | 54.4% | 41.7% |
| | Male | 386,231 | 56.5% | 41.1% | 44.4% | 57.0% |
| | Other | 9,187 | 1.3% | 1.3% | 1.2% | 1.3% |
| RUCA | Metro | 591,782 | 86.5% | 85.6% | 85.9% | 86.6% |
| | Micro | 52,231 | 7.6% | 8.2% | 7.8% | 7.6% |
| | Rural | 15,798 | 2.3% | 2.3% | 2.6% | 2.3% |
| | Small Town | 21,570 | 3.2% | 3.6% | 3.4% | 3.1% |
| | Unknown | 2,419 | 0.4% | 0.3% | 0.2% | 0.4% |
| SVI | Q1 | 67,520 | 9.9% | 11.2% | 11.8% | 9.8% |
| | Q2 | 99,195 | 14.5% | 16.4% | 16.1% | 14.4% |
| | Q3 | 112,787 | 16.5% | 17.6% | 17.1% | 16.5% |
| | Q4 | 152,524 | 22.3% | 22.2% | 22.6% | 22.3% |
| | Q5 | 247,654 | 36.2% | 32.1% | 31.9% | 36.4% |
| | Unknown | 4,120 | 0.6% | 0.5% | 0.5% | 0.6% |
| Age Group | 18-34 | 214,339 | 31.3% | 16.6% | 16.1% | 31.8% |
| | 35-49 | 206,714 | 30.2% | 31.0% | 31.9% | 30.2% |
| | 50-64 | 178,664 | 26.1% | 37.5% | 37.3% | 25.7% |
| | 65-74 | 59,742 | 8.7% | 12.0% | 12.0% | 8.6% |
| | 75+ | 24,341 | 3.6% | 2.9% | 2.7% | 3.6% |
| BMI | Underweight | 5,182 | 0.8% | 0.4% | 0.3% | 0.8% |
| | Healthy | 137,735 | 20.1% | 8.9% | 9.5% | 20.5% |
| | Overweight | 451,420 | 66.0% | 38.9% | 40.4% | 66.9% |
| | Obese | 405,024 | 59.2% | 77.2% | 80.3% | 58.6% |
| | Morbidly Obese | 99,656 | 14.6% | 39.7% | 40.1% | 13.7% |
| Ethnicity | Hispanic | 60,045 | 8.8% | 8.4% | 8.4% | 8.8% |
| Race | Black | 149,417 | 21.9% | 19.7% | 19.3% | 21.9% |
| MAUD | 1 | 57,313 | 8.4% | 9.2% | 10.0% | 8.3% |
| MNUD | 1 | 179,069 | 26.2% | 25.2% | 27.8% | 26.2% |
| MOUD | 1 | 65,266 | 9.5% | 6.8% | 7.3% | 9.6% |
| Anxiety | 1 | 332,200 | 48.6% | 62.4% | 61.8% | 48.1% |
| Depression | 1 | 317,652 | 46.5% | 60.2% | 60.1% | 46.0% |
| ADD/ADHD | 1 | 53,599 | 7.8% | 9.2% | 9.3% | 7.8% |
| Bipolar | 1 | 92,557 | 13.5% | 15.6% | 16.1% | 13.5% |
| Psychotic Disorders | 1 | 63,880 | 9.3% | 7.7% | 8.1% | 9.4% |
| PTSD | 1 | 65,828 | 9.6% | 12.0% | 13.1% | 9.5% |
| Diabetes | 1 | 114,105 | 16.7% | 49.5% | 48.6% | 15.6% |
| First OD Opioid | 1 | 123,554 | 18.1% | 17.9% | 17.6% | 18.1% |
| First OD Alcohol | 1 | 456,220 | 66.7% | 60.4% | 62.6% | 66.9% |
| First OD Stimulant | 1 | 30,927 | 4.5% | 3.7% | 3.7% | 4.5% |
| First OD Sedative | 1 | 43,159 | 6.3% | 10.0% | 9.5% | 6.2% |
| First OD Cannabinoid | 1 | 39,557 | 5.8% | 9.6% | 7.9% | 5.7% |
| First OD Cocaine | 1 | 29,039 | 4.2% | 4.2% | 4.1% | 4.2% |

| | | | | | | |
|---|---|---|---|---|---|---|
| First OD Hallucinogen | 1 | 5,233 | 0.8% | 0.4% | 0.4% | 0.8% |

## Table 2. Risk of Repeat Overdose by GLP-1 Status

| Exposure | GLP-1 Use | Risk | Lower CI | Upper CI |
|---|---|---|---|---|
| Overall | Active GLP-1 | 0.613 | 0.554 | 0.679 |
| | Discontinued GLP-1 | 0.799 | 0.741 | 0.861 |
| Alcohol | Active GLP-1 | 0.604 | 0.536 | 0.680 |
| | Discontinued GLP-1 | 0.819 | 0.750 | 0.895 |
| Non-Alcohol | Active GLP-1 | 0.627 | 0.516 | 0.761 |
| | Discontinued GLP-1 | 0.764 | 0.660 | 0.883 |
| No Treatment Meds | Active GLP-1 | 0.562 | 0.482 | 0.654 |
| | Discontinued GLP-1 | 0.721 | 0.646 | 0.805 |