How do GLP-1 receptor agonist medications compare to standard treatment in reducing cannabis use and associated symptoms among individuals with cannabis use disorder?

Semaglutide shows promising associations with reduced cannabis use disorder diagnoses in observational data, but randomized controlled trials are needed to establish whether GLP-1 receptor agonists effectively reduce cannabis use and symptoms.

Abstract

One retrospective cohort study of 681,268 patients across two populations (obesity and type 2 diabetes) examined semaglutide compared to non-GLP-1RA anti-obesity or anti-diabetes medications. In patients with obesity, semaglutide was associated with a 44% lower risk of incident cannabis use disorder (HR: 0.56, 95% CI: 0.42-0.75) and a 38% lower risk of recurrent CUD (HR: 0.62, 95% CI: 0.46-0.84) over 12 months. Similar findings emerged in the type 2 diabetes population for incident CUD (HR: 0.40, 95% CI: 0.29-0.56), though the association with recurrent CUD did not reach statistical significance (HR: 0.66, 95% CI: 0.42-1.03). Effects were consistent across gender and age subgroups but not observed in Black patients. However, the retrospective design precludes causal inferences, and critical information is unavailable including safety data, baseline cannabis use patterns, specific dosing protocols, and validated CUD severity measures beyond diagnostic codes. While these findings suggest a potential association between semaglutide and reduced CUD diagnoses in real-world populations, randomized controlled trials with comprehensive cannabis use assessments are needed to establish efficacy and safety of GLP-1 receptor agonists for treating cannabis use disorder.

Paper search

We performed a semantic search using the query ”How do GLP-1 receptor agonist medications compare to standard treatment in reducing cannabis use and associated symptoms among individuals with cannabis use disorder?” across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We retrieved the 50 papers most relevant to the query.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Cannabis Use Disorder Population**: Do the study participants have a formal diagnosis of cannabis use disorder according to established diagnostic criteria (DSM-5, ICD-11, or equivalent clinical assessment)?
- **GLP-1 Receptor Agonist Intervention**: Does the study evaluate a GLP-1 receptor agonist medication (e.g., semaglutide, liraglutide, exenatide, dulaglutide) as the primary intervention for cannabis use disorder?
- **Cannabis Use Outcomes**: Does the study report quantitative measures of cannabis use reduction (e.g., frequency of use, quantity consumed, abstinence rates, urinalysis results) or associated symptoms (e.g., withdrawal symptoms, craving scores)?
- **Study Design**: Is the study a controlled design (randomized controlled trial, quasi-experimental study, controlled clinical trial, systematic review, or meta-analysis) with an appropriate comparison group?
- **Human Participants**: Was the study conducted in human participants (not animal studies)?
- **Publication Completeness**: Is this a full-text publication with complete results (not a conference abstract, protocol, or duplicate publication of previously included data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **GLP-1 Intervention**:

  Extract details about the GLP-1 receptor agonist medication used for reducing cannabis use in individuals with cannabis use disorder, including:

- Specific GLP-1RA drug name (e.g., semaglutide, liraglutide, dulaglutide)
- Dose and dosing schedule
- Route of administration (subcutaneous, oral)
- Duration of treatment
- Original indication for prescription (diabetes, weight management, other)
- Any dose adjustments or titration protocols

- **Comparison Treatment**:

  Extract details about the standard/comparison treatment used for cannabis use disorder, including:

- Type of comparison (placebo, usual care, non-GLP-1RA medications, behavioral interventions)
- Specific medications if applicable (names, doses, duration)
- Behavioral or psychosocial interventions if included
- Treatment intensity and duration
- Whether comparison represents typical standard of care for CUD in the study setting

- **Cannabis Outcomes**:

  Extract all cannabis use and cannabis use disorder outcomes measured, including:

- Cannabis use frequency measures (days used, times per day, abstinence periods)
- Cannabis quantity measures (grams consumed, number of joints/sessions)
- CUD diagnostic criteria or severity measures (DSM-5 criteria, CUDIT scores)
- Cannabis craving or urges assessments
- Cannabis withdrawal symptoms
- Time to cannabis use reduction or cessation
- Relapse or recurrence measures
- How outcomes were assessed (self-report, urine tests, clinical interview)

- **Study Population**:

  Extract characteristics of individuals with cannabis use disorder in the study, including:

- Baseline CUD severity (mild, moderate, severe; DSM-5 criteria count)
- Cannabis use patterns at baseline (frequency, quantity, duration of use)
- Demographics (age range, gender distribution, race/ethnicity)
- Psychiatric comorbidities (depression, anxiety, ADHD, other substance use disorders)
- Medical comorbidities (diabetes, obesity, other conditions)
- Previous CUD treatment history

- Concurrent medications or treatments
- Sample size for each treatment group

- **Study Design**:

  Extract study methodology details relevant to comparing GLP-1RA with standard treatment for cannabis use disorder, including:

- Study type (RCT, cohort, case-control, retrospective analysis)
- Randomization and blinding procedures if applicable
- Inclusion/exclusion criteria specific to CUD population
- Primary and secondary endpoint definitions
- Statistical analysis approach for treatment comparison
- Confounding control methods (matching, adjustment variables)
- Risk of bias or quality assessment factors

- **Comparative Results**:

  Extract quantitative results comparing GLP-1 receptor agonists to standard treatment for cannabis-related outcomes, including:

- Effect sizes with confidence intervals (hazard ratios, odds ratios, mean differences)
- Statistical significance (p-values)
- Absolute risk differences or number needed to treat
- Response rates or success rates for each group
- Time-to-event outcomes (time to cannabis reduction, relapse)
- Subgroup analyses by baseline characteristics
- Whether results favored GLP-1RA, standard treatment, or showed no difference

- **Follow-up Duration**:

  Extract the duration of observation for cannabis use disorder outcomes, including:

- Total follow-up period for primary outcomes
- Follow-up periods for different outcome measures if they vary
- Timing of outcome assessments (weekly, monthly, quarterly)
- Loss to follow-up rates for each treatment group
- Whether long-term sustainability of effects was assessed
- Any post-treatment follow-up period after medication discontinuation

- **Safety Profile**:

  Extract safety and tolerability data comparing GLP-1 receptor agonists to standard treatment in cannabis use disorder patients, including:

- Adverse event rates for each treatment group
- Specific side effects related to GLP-1RAs (nausea, vomiting, gastrointestinal effects)
- Serious adverse events
- Discontinuation rates due to adverse effects
- Drug interactions or contraindications
- Monitoring requirements
- Any cannabis use disorder-specific safety considerations

- **Study Context**:

  Extract contextual factors affecting generalizability of GLP-1RA vs. standard treatment comparison for cannabis use disorder, including:

- Healthcare setting (primary care, specialty addiction clinic, hospital)
- Geographic location and healthcare system type
- Study period (years when conducted)
- Regulatory status of cannabis in study location
- Availability of standard CUD treatments in study setting
- Provider expertise and training
- Insurance coverage or cost considerations
- Cultural or demographic factors affecting treatment acceptance

Results

Characteristics of Included Studies

This systematic review identified one retrospective cohort study examining the association between GLP-1 receptor agonist medications and cannabis use disorder outcomes.

Study	Full text retrieved?	Study type	Population	Sample size	Study period	Geographic location	Follow-up duration
William Wang et al., 2024	Yes	Retrospective cohort study	Patients with obesity or type 2 diabetes	Obesity cohort: 85,223 (45,445 semaglutide, 37,744 non-GLP-1RA)T2D cohort: 596,045 (25,843 semaglutide, 562,006 non-GLP-1RA)	Obesity: June 2021-December 2022T2D: December 2017-May 2021	61 large healthcare organizations in the US	12 months primary outcome1-3 years for T2D population

The study utilized electronic health records from the TriNetX Analytics Network, encompassing approximately 105.3 million patients across diverse healthcare settings in the United States. The intervention consisted of semaglutide, a GLP-1 receptor agonist originally indicated for type 2 diabetes and weight management. The comparison groups received non-GLP-1RA anti-obesity medications in the obesity cohort and non-GLP-1RA anti-diabetes medications in the T2D cohort. Specific dosing schedules and route of administration were not reported.

The study populations had distinct demographic characteristics. In the obesity cohort, the mean age was 51.3 years with 65.6% women. The T2D cohort had a mean age of 58.0 years with 45.4% women. The semaglutide cohort showed higher prevalence of medical comorbidities (morbid obesity and T2D) but lower prevalence of psychiatric comorbidities compared to non-GLP-1RA cohorts. Propensity score matching was employed to balance cohorts on potential risk factors for cannabis use disorder.

The study assessed cannabis use disorder outcomes using ICD-10 diagnostic codes from electronic health records and medical encounters, examining both incident CUD in patients with no prior CUD diagnosis and recurrent CUD in patients with prior CUD history. Specific measures of cannabis use frequency, quantity, craving, or withdrawal symptoms were not reported.

Effects

Primary Outcomes in Obesity Population

Outcome	Semaglutide absolute risk	Non-GLP-1RA absolute risk	Hazard ratio (95% CI)	Statistical significance
Incident CUD	0.28%	0.48%	0.56 (0.42-0.75)	Yes (CI excludes 1)
Recurrent CUD	13.0%	20.4%	0.62 (0.46-0.84)	Yes (CI excludes 1)

In patients with obesity, semaglutide demonstrated a 44% reduction in risk for incident cannabis use disorder compared to non-GLP-1RA anti-obesity medications (HR: 0.56, 95% CI: 0.42-0.75). The absolute risk difference was 0.20 percentage points, with incident CUD occurring in 0.28% of semaglutide patients versus 0.48% of comparison patients. For recurrent CUD in patients with prior CUD history, semaglutide showed a 38% risk reduction (HR: 0.62, 95% CI: 0.46-0.84), with absolute risks of 13.0% versus 20.4%, representing a 7.4 percentage point difference.

Primary Outcomes in Type 2 Diabetes Population

Outcome	Semaglutide absolute risk	Non-GLP-1RA absolute risk	Hazard ratio (95% CI)	Statistical significance
Incident CUD	0.21%	0.48%	0.40 (0.29-0.56)	Yes (CI excludes 1)
Recurrent CUD	13.7%	19.1%	0.66 (0.42-1.03)	No (CI includes 1)

The findings in the type 2 diabetes population replicated and extended those observed in the obesity cohort. Semaglutide showed a 60% reduction in incident CUD risk compared to non-GLP-1RA anti-diabetes medications (HR: 0.40, 95% CI: 0.29-0.56), with absolute risks of 0.21% versus 0.48%. For recurrent CUD, the hazard ratio was 0.66 (95% CI: 0.42-1.03), though the confidence interval crossed 1.0, indicating the finding did not reach conventional statistical significance. Absolute risks were 13.7% for semaglutide versus 19.1% for comparison medications.

Subgroup Analyses

Subgroup analyses stratified by gender, age group, and race demonstrated consistent reductions in CUD risk with semaglutide across most demographic categories. The exception was Black patients, where the protective effect was not observed. This finding warrants particular attention given the disproportionate impact of cannabis use disorder

and the regulatory environment affecting access to both cannabis and medical treatments across different racial and ethnic communities.

Long-term Outcomes

In the type 2 diabetes population, longer-term associations were examined at 1, 2, and 3 years following the index event. However, specific hazard ratios for these extended follow-up periods were not reported in the available extractions.

Safety and Tolerability

The study did not report specific safety and tolerability data comparing semaglutide to non-GLP-1RA medications in patients with cannabis use disorder. Adverse event rates, discontinuation rates due to adverse effects, and GLP-1RA-specific side effects were not documented. The authors noted concerns about potential interactions between cannabis use and semaglutide's therapeutic effects but stated there was no evidence of such interactions or reduced efficacy.

Methodological Considerations

The retrospective cohort design prevents causal inferences. Despite propensity score matching on potential CUD risk factors, unmeasured confounding remains possible. The study relied on ICD-10 diagnostic codes rather than validated CUD assessment instruments, which may affect outcome ascertainment. No information was available on baseline CUD severity, cannabis use patterns, or previous CUD treatment history, limiting ability to assess treatment effects across different patient subgroups.

The study setting encompassed diverse healthcare organizations across the United States during a period of expanding cannabis legalization. Current treatment for CUD involves tapering marijuana use and behavioral interventions, with no FDA-approved medications available. This context suggests semaglutide may represent a novel pharmacological option, though the study design cannot determine whether observed associations reflect direct effects on cannabis-related neurocircuitry or indirect effects through metabolic pathways.

Loss to follow-up rates were not reported, and specific details on dose, dosing schedule, and route of administration were not provided. The 12-month primary follow-up period is substantial but may not capture long-term sustainability of effects or outcomes following medication discontinuation, as no post-treatment follow-up was reported.

References

William Wang, Nora D. Volkow, Nathan A. Berger, P. Davis, D. Kaelber, and R. Xu. "Association of Semaglutide with Reduced Incidence and Relapse of Cannabis Use Disorder in Real-World Populations: A Retrospective Cohort Study." *Molecular Psychiatry*, 2024.