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Weighing Risks: Do GLP-1s Impact the Mind?

Glucagon-Like Peptide-1 Receptor Agonists and Risk of Suicidality Among Patients with Type 2 Diabetes: Active Comparator, New User Cohort Study

Shapiro SB, Yin H, Hoi Yun Yu O, et al. Glucagon-like peptide-1 receptor agonists and risk of suicidality among patients with type 2 diabetes: active comparator, new user cohort study. *BMJ*. 2025;388:e080679.doi:10.1136.

KEY TAKEAWAY: The use of glucagon-like peptide-1 (GLP1) receptor agonists among patients with type 2 diabetes mellitus (T2DM) does not increase the risk of suicide compared to dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

STUDY DESIGN: Two new user, active comparator, retrospective cohort studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to non-randomized cohort study and short duration of study follow up)

BRIEF BACKGROUND INFORMATION: GLP-1 receptor agonists are widely prescribed and discussed in media and patient-physician encounters. The initial clinical trials for GLP-1 receptor agonists showed no evidence of increased suicidality, but some observational studies generated varied results on risk of suicidality and/or self-harm. There is a theoretical risk of increased suicidality as GLP-1 receptor agonists may cause hyperactivity of the hypothalamic pituitary adrenal axis. These large cohort studies evaluated possible suicidality in new users of GLP-1 receptor agonists compared with DPP-4 and SGLT-2 inhibitors, which are commonly prescribed at similar stages of T2DM.

PATIENTS: Adults with T2DM

INTERVENTION: GLP1 receptor agonists

CONTROL: DPP-4 inhibitors in one cohort and SGLT-2 inhibitors in the other

PRIMARY OUTCOME: Suicidality defined as composite of suicidal ideation, self-harm hospitalization, or completed suicide

Secondary Outcome: Suicidal ideation, hospital admission for self-harm, suicide considered separately

METHODS (BRIEF DESCRIPTION):

- Investigators analyzed adults (≥18 years old) with a diagnosis of T2DM from the UK Clinical Practice Research Datalink (CPRD) GOLD and Aurum primary care databases for whom their physician prescribed a GLP-1. The CPRD includes 60 million patients from 2,000 general practices in the United Kingdom).
- GLP-1 drugs comprised dulaglutide, exenatide, liraglutide, lixisenatide, and senaglutide.
- Exclusion criteria included diabetes diagnosis for <1 year, use of GLP-1 for weight loss, end-stage renal disease, multiple endocrine neoplasia, or concurrent use of GLP-1 and another study drug.
- DPP-4 agents comprised aloglipin, linagliptin, saxagliptin, sitagliptin, or vildagliptin.
- SGLT-2 agents comprised canagliflozin, dapagliflozin, empagliflozin, and ertagliflozin.
- Physicians prescribed a GLP-1 or a DPP-4 between January 1, 2007 and December 2020 for the first cohort, with the second cohort comprising SGLT-2 inhibitors prescribed between January 1, 2013 and December 31, 2020.
- Investigators defined suicidality as a composite of suicidal ideation identified in the CPRD, hospital admission for self-harm based on the Hospital Episode Statistics Admitted Patient Care (HES APC) database, or completed suicide as identified in the Office for National Statistics (ONS) database.
- Weighted hazard ratios were calculated for the primary and secondary outcomes with 95% confidence intervals by considering potential confounders such as age, sex, socioeconomic status, body mass index, and factors other factors previously associated with suicidality including insomnia, epilepsy, dementia, chronic pain, history of cancer, and substance use).
- Researchers estimated hazard ratios (HR) and 95% confidence intervals using statistics to adjust crude outcomes data for confounders between GLP-1 and control groups (such as differences in body mass index [BMI], hemoglobin A1C levels). The models included using propensity score, fine stratification, and weighted Cox proportional hazards to arrive at the adjusted HR.

INTERVENTION (# IN THE GROUP):

- GLP1 Cohort 1: 36,082
- GLP1 Cohort 2: 32,336

COMPARISON (# IN THE GROUP):

- DPP-4 inhibitors Cohort 1: 234,028
- SGLT-2 inhibitors Cohort 2: 96,212

FOLLOW-UP PERIOD:

- The first cohort of GLP-1 receptor agonist users: Median 1.3 years
- First cohort of DPP-4 inhibitor users: Median 1.7 years.
- Second cohort of both GLP-1 and SLGT2 receptor users: Median 1.3 years

RESULTS:

Primary Outcome –

- GLP-1 receptor agonists did not increase the risk of suicidality compared to DPP-4 inhibitors (weighted hazard ratio [wHR] 1.0; 95% CI, 0.85–1.2).
- GLP-1 receptor agonists did not increase the risk of suicidality compared to SGLT-2 inhibitors (wHR 0.91; 95% CI, 0.73–1.1).

Secondary Outcome –

- Using GLP-1 receptor agonists was not associated with suicidal ideation, self-harm, and suicide as separate outcomes when compared with DPP-4 inhibitors or SGLT-2 inhibitors.

LIMITATIONS:

- There is the possibility for misclassification of outcomes and interventions due to the CPRD records being based on the prescriptions written by general practitioners, which may not be filled by patients.
- The primary analysis of self-harm was identified through hospital admissions, documenting the most extreme situations but possibly not detecting outpatient concerns.
- There may be other confounding factors not considered by the researchers.
- The follow-up period was short, limiting the potential to detect long-term effects.

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Once-Weekly Semaglutide for MASH: Liver and Metabolic Gains

Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis

Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med.* 2025;392(21):2089-2099. doi:10.1056/NEJMoa2413258

KEY TAKEAWAY: Treatment with once weekly semaglutide improves metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, with additional metabolic benefits.

STUDY DESIGN: Multicenter, double-blind, randomized, placebo-controlled phase three clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to disease-oriented outcomes)

BRIEF BACKGROUND INFORMATION: MASH is a progressive liver disease associated with fibrosis, cirrhosis, and hepatocellular carcinoma. Current treatments are limited, but semaglutide, a GLP-1 receptor agonist FDA-approved for diabetes and obesity, has previously shown promise for treating MASH. This trial assessed if semaglutide therapy resulted in histologic improvement in the treatment of liver fibrosis and MASH.

PATIENTS: Adults with MASH and liver fibrosis

INTERVENTION: Semaglutide

CONTROL: Placebo

PRIMARY OUTCOME: Resolution of steatohepatitis without worsening of fibrosis and improvement in fibrosis without worsening of steatohepatitis

Secondary Outcome: Combined fibrosis improvement and steatohepatitis resolution, percent change in body weight, safety

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with biopsy-proven steatohepatitis and liver fibrosis stage two or three and nonalcoholic fatty liver disease score (NAS) of ≥4 were enrolled in this double blind, randomized trial across 253 clinical sites in 37 countries.
    - Liver fibrosis was staged according to the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) classification. Score range from 0–4, with a score of four indicative of cirrhosis.
    - Severity of steatohepatitis is estimated with the NAS score, which incorporates levels of lobular inflammation and hepatocyte ballooning. Scores range from 0–8, with scores of ≥5 indicating steatohepatitis and scores of ≤3 ruling out the diagnosis.
- Patients with chronic liver disease other than MASH, average alcohol consumption >20 g per day for women or >30 g per day for men, hepatic decompensation, liver enzymes >5 times the upper limit of normal, chronic kidney disease stage ≥4, uncontrolled diabetes (hemoglobin A1C >9.5%), or history of pancreatitis were excluded.
- Participants were 56 years old on average, with a mean BMI of 35. 57% were female, 68% identified as White and most (69%) participants had stage three fibrosis.
- Eligible participants were randomized in a 2:1 ratio to receive subcutaneous semaglutide or placebo weekly.
- The dose of semaglutide was titrated every four weeks from a starting dose of 0.25 mg weekly, to the target dose of 2.4 mg weekly.
- Two liver biopsies were completed on each participant, including during the screening period and at week 72 after randomization.
- The primary outcomes included:
    - Resolution of steatohepatitis without worsening of fibrosis. NAS score of 0 for ballooning and 0–1 for inflammation was defined as resolution of steatohepatitis
    - Improvement in fibrosis without worsening of steatohepatitis. Reduction by one stage on the NASH CRN fibrosis scale indicated fibrosis improvement
- Secondary outcomes include combined fibrosis improvement and steatohepatitis resolution, percent change in body weight, and adverse effects.

INTERVENTION (# IN THE GROUP): 534

COMPARISON (# IN THE GROUP): 266

FOLLOW-UP PERIOD: 72 weeks

RESULTS:

Primary Outcome –

- Semaglutide improved resolution of steatohepatitis with no worsening of liver fibrosis compared to placebo (63% vs 34%, respectively; estimated difference [ED] 29%; 95% CI, 21–36).
- Semaglutide reduced liver fibrosis without worsening steatohepatitis compared to placebo (37% vs 22%, respectively; ED 14%; 95% CI, 7.5–21).

Secondary Outcome –

- Semaglutide group resolved steatohepatitis and reduced fibrosis compared to placebo (33% vs 16%, respectively; ED 17%; 95% CI, 10–23).
- Semaglutide group resulted in higher weight loss compared to placebo (–11% vs –2.0%, respectively; ED –8.5%; 95% CI, –9.6 to –7.4).
- Most patients (84%) tolerated the goal dose of semaglutide 2.4 mg weekly.
- Adverse events were reported by 86% of participants on semaglutide and 80% of those with placebo, with premature discontinuation by 2.6% of patients taking semaglutide and 3.3% of patients taking placebo.
- Adverse gastrointestinal (GI) events were reported in both groups, but nausea, vomiting, diarrhea and constipation were more common in the semaglutide group.
- Rates of pancreatitis were similar between the groups.

LIMITATIONS:

- The data presented is interim analysis for an ongoing trial, with longer-term liver-related outcomes pending.
- The trial included a smaller number of patients that are people of color, potentially limiting generalizability.
- Several patients did not complete the liver biopsy at 72 weeks, leading to 12% in the semaglutide group and 16% in the placebo group with missing data.
- Changes in body composition during therapy were not accounted for, as this intervention may result in reduction in lean mass or muscle.

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GLP-1 Dropouts: More Common Without Diabetes

Discontinuation and Reinitiation of Dual-Labeled GLP-1 Receptor Agonists Among US Adults with Overweight or Obesity

Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and Reinitiation of Dual-Labeled GLP-1 Receptor Agonists Among US Adults With Overweight or Obesity. *JAMA Netw Open.* 2025;8(1):e2457349. Published 2025 Jan 2. doi:10.1001/jamanetworkopen.2024.57349

KEY TAKEAWAY: Patients without diabetes discontinue their glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy significantly more and restart their GLP-1 RA significantly less than those with type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: GLP-1 RAs have shown to help with weight loss and management of diabetes. There is a wide reported range of GLP-1 RA discontinuation rates. This study aimed to assess the common causes of discontinuation and re-initiation of GLP-1 RA in patients with and without T2DM.

PATIENTS: Adult who used GLP-1 RAs and were overweight or obese

INTERVENTION: Presence of T2DM

CONTROL: Absence of T2DM

PRIMARY OUTCOME: Both the discontinuation and re-initiation rates of GLP-1 RAs

METHODS (BRIEF DESCRIPTION):

- Adults (≥18 years old) who used GLP-1 RAs (liraglutide, semaglutide, or tirzepatide) for the first time and were overweight or obese with a BMI of ≥27 were included in the study.
  - Participants were followed for two years for discontinuation rate and an additional two years for re-initiation rate.
- De-identified patient records were obtained from a large nationwide database. Patients' vitals, lab results, medication prescriptions, and clinical notes were used to further stratify the population.
- Patients were labeled as having T2DM based on their A1C, diagnosis code, or use of insulin or a dipeptidyl peptidase 4 inhibitor.
- The comparison group did not have diabetes.
- The dispense date of the first GLP-1 RA was recorded as the initiation date. If a patient went ≥60 days without filling a GLP-1 RA, this was considered a primary discontinuation.
- If a patient filled a GLP-1 RA after primary discontinuation, this was considered a re-initiation.

INTERVENTION (# IN THE GROUP): 76,524

COMPARISON (# IN THE GROUP): 48,950

FOLLOW-UP PERIOD: Up to four years

RESULTS:

Primary Outcome –

- Patients without T2DM had a significantly higher discontinuation rate of GLP-1 RAs at two years (84%; 95% CI, 84–85) than patients with type 2 diabetes (64%; 95% CI, 64–65).
- More weight loss was associated with a lower rate of discontinuation of GLP-1 RAs in patients with T2DM and without T2DM.
  - Patients with T2DM (HR 3.1%; 95% CI, 2.9–3.2)
  - Patients without T2DM (HR 3.3%; 95% CI, 3.2–3.5)
- Moderate or severe gastrointestinal (GI) side effects were associated with an increased probability of discontinuation in patients with and without T2DM.
  - Patients with T2DM (HR 1.4; 95% CI, 1.3–1.5)
  - Patients without T2DM (HR 1.2; 95% CI, 1.1–1.3)
- In patients who discontinued their GLP-1 RA, the two-year re-initiation rate was less in those without type 2 diabetes than those with type 2 diabetes
  - Patients with T2DM (57%; 95% CI, 57–58)
  - Patients without T2DM (46%; 95% CI, 45–47)
- In patients who regained 1% of weight after discontinuing the GLP-1 RA initially, there was an increased rate of restarting the medication in those with and without T2DM.
  - Patients with T2DM (HR 2.3%; 95% CI, 1.9–2.8)
  - Patients without T2DM (HR 2.8%; 95% CI, 2.4–3.2)

LIMITATIONS:

- GLP-1 RA shortages were not accounted for in the study.
- Mild GI side effects were not accounted for in the study.

- Patients who did not have a weight documented within 60 days of stopping their GLP-1 RA were not analyzed.
- Patients skipping or rationing their medication was not accounted for.

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