

MEDBRIEF

FDA Data Reveal Different Risks for GLP-1s

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✦ Summary

FDA data analysis reveals GLP-1s have distinct adverse event patterns, varying by treatment and indication. Notable risks include gastrointestinal, psychiatric, and nutritional disorders, with specific profiles for each GLP-1 medication.

TOPLINE:

Analysis of real-world pharmacovigilance data shows that GLP-1s demonstrate distinct adverse event patterns across indications, primarily related to metabolic, nutritional, gastrointestinal, and psychiatric disorders, with different profiles observed across treatments.

METHODOLOGY:

- With the rapid uptake of GLP-1s, postmarketing surveillance is essential to detecting safety signals not captured in clinical trials.
- Researchers conducted a retrospective analysis of the US FDA Adverse Event Reporting System (FAERS) database from 2012 to 2025, focusing on five commonly prescribed GLP-1s: exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide.
- Subgroup analyses compared adverse event associations by indication (type 2 diabetes [T2D] vs weight control or obesity), GLP-1s vs other drugs (DPP-4 and SGLT2 inhibitors), and specific to individual GLP-1s.

- Safety signals were identified using disproportionality analyses, including reporting odds ratios (RORs) and proportional reporting ratios.

TAKEAWAY:

- The analysis included 137,451 cases involving GLP-1s, most often for T2D treatment (42,570 cases) and weight control or obesity (12,311 cases).
- Compared with DPP-4 and SGLT2 inhibitors, GLP-1s were associated with increased reporting of several adverse events, including skin and subcutaneous conditions (ROR, 37.24); flatulence, bloating, and distension (ROR, 4.81); gastrointestinal and abdominal pain (ROR, 2.37); alopecia (ROR, 2.40); taste disorders (ROR, 4.83); general nutritional disorders (ROR, 2.61); and suicidal or self-injurious behaviors (ROR, 2.68).
- In T2D, GLP-1 use was associated with retinopathies (ROR, 19.73), skin and subcutaneous conditions (ROR, 19.75), pancreatic neoplasms (ROR, 4.05), hearing losses (ROR, 5.45), and cataracts (ROR, 4.43).
- For weight control or obesity, GLP-1 use was associated with general nutritional disorders (ROR, 3.08), sensory abnormalities (ROR, 6.28), panic attacks and disorders (ROR, 4.63), suicidal or self-injurious behavior (ROR, 4.64), depressive disorders (ROR, 2.79), immune-associated conditions (ROR, 3.13), and eating disorders (ROR, 2.53). Among female patients, GLP-1s were linked to the reporting of menstrual bleeding, ovarian or fallopian cysts and neoplasms, and reproductive system hemorrhages.
- Individual GLP-1s showed varying toxicity profiles. Semaglutide was associated with more gastrointestinal and psychiatric events, dulaglutide and exenatide with more deaths and hospitalizations, and liraglutide and exenatide with more neoplasm-related reports. Gastrointestinal disorders were common across all GLP-1s.

IN PRACTICE:

“As millions of patients are taking GLP-1s for weight control and obesity

treatment worldwide, clinicians should be vigilant in monitoring for unanticipated long-term adverse effects,” the authors of the study wrote.

SOURCE:

The study was led by David Stone, Departments of Oncological Sciences and Biomedical Informatics, University of Utah, Salt Lake City. It was [published online](#) in *Obesity*.

LIMITATIONS:

The FAERS database is limited by underreporting and differential reporting bias. Reports may be incomplete and contain missing data, which may limit the ability to establish associations between drugs and adverse events. Clinical details in the database may also be limited.

DISCLOSURES:

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GLP-1 Drugs Under Scrutiny: How Real Are the Risks?

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GLP-1 receptor agonists (RAs) are established therapies for glycemic control in [type 2 diabetes](#) (T2D) and [for weight loss](#), with growing evidence supporting broader cardiometabolic benefits. Their expanding use requires careful evaluation of efficacy, tolerability, and safety across diverse populations, particularly because [adverse effects and discontinuation rates](#) remain clinically relevant considerations.

[Obesity](#) is recognized as a chronic disease and a central component of the cardiometabolic spectrum. Evidence supports the clinical benefits of GLP-1 RAs for weight management and improvement in cardiovascular and metabolic risk profiles. The therapeutic role of this drug class is therefore extending beyond glycemic control and weight loss. Although these agents were developed to mimic peripheral GLP-1 activity, their effects on weight reduction depend largely on reduced energy intake [mediated through central nervous](#) system pathways.

GLP-1 RAs exert [anti-inflammatory effects](#) across multiple organ systems, including the lungs, cardiovascular system, liver, intestine, kidneys, joints, and central nervous system. Preclinical and clinical evidence supports these effects in the cardiovascular system, liver, kidneys, and joints.

Neuroprotective mechanisms include reduced protein aggregation, enhanced autophagy, improved mitochondrial function, suppression of neuroinflammation, and preservation of synaptic integrity. Epidemiologic analyses suggest a reduced incidence of [dementia](#), [Parkinson disease](#), and [multiple sclerosis](#) among long-term users. However, anti-inflammatory effects in the central nervous system, lungs, and intestine remain incompletely defined and require further study, particularly in the context of [safety and tolerability](#).

Therapeutic Tolerability

A systematic review of 39 randomized controlled trials demonstrated a class effect, with increased risk for nausea, vomiting, [diarrhea](#), and [constipation](#) compared with placebo in [individuals without diabetes](#). Gastrointestinal adverse events frequently led to treatment discontinuation in both clinical trials and real-world settings. Discontinuation rates were 6.5% among individuals receiving GLP-1 RAs compared with 3.6% of those receiving placebo. Nausea was the most common reason for discontinuation, followed by vomiting and diarrhea. Risks for constipation, abdominal discomfort, and pain were lower. Slower and [more flexible titration](#) of dose improved adherence and reduced adverse events without compromising efficacy, although optimal titration strategies require further study.

GI Symptom Assessment

Most studies assessed symptoms through self-reporting by participants. Although practical, [this approach has limitations](#). Future research should incorporate validated tools to assess upper [gastrointestinal symptom severity](#).

GI Motility

The [incidence of retained gastric content](#) was 56% of individuals receiving GLP-1 RAs compared with 19% of those not receiving these agents. [Although studies reported](#) an increased risk for retained gastric content leading to premature [endoscopy discontinuation](#), no increased risk for [aspiration pneumonia](#) was identified. These findings indicate a clear association between GLP-1 RA therapy and risk for gastric retention

without evidence of increased aspiration risk.

This observation has prompted consideration of whether GLP-1 RA therapy should be modified or withheld before procedures associated with aspiration risk. Current multisociety guidance recommends an individualized approach.

Underlying Mechanisms

Gastrointestinal adverse events associated with GLP-1 RAs reflect altered gastrointestinal function. GLP-1 receptor activation slows gastric emptying and suppresses small intestinal motility. In addition, direct interaction with receptors in brainstem regions such as the [area postrema and nucleus of the solitary tract](#) may contribute to nausea through activation of the chemosensitive zone.

Biliary Complications

A systematic review of 55 double-blind randomized controlled trials showed that treatment with GLP-1 RAs was associated with an increased risk for [cholelithiasis](#) compared to placebo (risk ratio, 1.46), but no increased risk for [cholecystitis](#), [cholangitis](#), or [pancreatitis](#). Retrospective analyses suggest that early concerns linking GLP-1 RAs to [acute pancreatitis](#) were influenced by the diagnostic criteria applied. These criteria require two of three features: severe upper abdominal pain radiating to the back, an [elevated amylase](#) or [lipase](#) level, and characteristic imaging findings. Treatment with GLP-1 RAs is known to cause abdominal symptoms in many patients and may also lead to elevated [amylase](#) or lipase levels that do not predict clinical acute pancreatitis.

This context helps explain how misclassification may have occurred and supports the presence of reporting bias in adverse event databases, particularly when a serious safety signal emerges. The findings underscore the need for robust pharmacovigilance research when evaluating suspected adverse events associated with newer therapies.

Thyroid Cancer

An increased risk for medullary [thyroid carcinoma](#) with GLP-1 RAs has been

An increased risk for medullary [thyroid carcinoma](#) with GLP-1 RAs has been hypothesized in susceptible individuals, although this signal has not been established in otherwise healthy populations.

An analysis of 93 phase 2 and 3 trials of [liraglutide](#) and [semaglutide](#), supported by postmarketing surveillance data, found no association between GLP-1 RA use and the risk for [thyroid cancer](#) in adults. However, a personal or family history of [medullary thyroid carcinoma](#) or [multiple endocrine neoplasia type 2](#) remains a contraindication to GLP-1 RA therapy.

Retinopathy and Other Vision Problems

Subcutaneous semaglutide was associated with more retinopathy complications in the SUSTAIN-6 cardiovascular outcomes trial. A retrospective review suggests this may reflect the larger reductions in plasma glucose and [A1c](#) achieved with [semaglutide compared](#) with standard therapy. Ongoing studies are assessing its effects on retinopathy progression.

[Nonarteritic anterior ischemic optic neuropathy](#) is a sudden, painless cause of vision loss that occurs mainly in individuals with T2D. It results from hypoperfusion of the posterior ciliary arteries supplying the optic nerve head, leading to ischemic injury and optic disc edema. [Risk increases with age](#) and vascular comorbidities, including [hypertension](#), T2D, hyperlipidemia, [obstructive sleep apnea](#), and optic disc abnormalities. Reported links with GLP-1 RAs are based on retrospective data, which do not establish causality and are prone to confounding. The association may reflect underlying risk factors rather than drug effects. A [meta-analysis](#) of 20 randomized controlled trials found no association between GLP-1 RA use and risk for optic nerve or vision related events.

Depression and Psychiatric Outcomes

A systematic review of 80 randomized clinical trials found no association between GLP-1 RA use and [major depression, suicide, or psychosis](#). Treatment with GLP-1 RAs was also associated with better mental health-related quality of life.

Effects in Specific Populations

Younger individuals

A meta-analysis of five studies in younger individuals with T2D showed higher adverse event rates with GLP-1 RAs, but [low discontinuation rates](#).

Pregnancy

In animal studies, GLP-1 RA exposure was associated with reduced fetal growth, delayed skeletal ossification, and lower maternal weight gain and food intake. Use is not recommended during pregnancy or when planning pregnancy.

Severe renal impairment

[Gastrointestinal adverse effects](#) are more common in people with severe renal impairment, and use of GLP-1 RAs should be individualized after weighing risks and benefits.

Older adults

Discontinuation rates of GLP-1 RAs are high in this population. After 24 months, 68.2% of individuals younger than 65 years discontinued therapy, rising to 75.3% in those aged 65-74 years and 82.6% in those aged 75 years or older. Reasons include cost, variable efficacy, patient preference, and adverse gastrointestinal effects. [Bone loss](#) has been reported with semaglutide, although exercise may reduce this risk. These risks should be balanced against cardiovascular benefit, which increases with age.

Muscle mass reduction

Weight loss with GLP-1 RAs includes loss of lean body mass, raising [concern for sarcopenia](#). Evidence linking this to reduced physical function remains limited. Caution is warranted in higher-risk groups, including older adults and those with low physical activity, low protein intake, or rapid weight loss.

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