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GI Adverse Events with GLP-1 Receptor Agonists for Weight Loss: Understanding the Risks

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GENERAL GI

This summary reviews Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M. Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. JAMA Medicine 2023; In Press. doi:10.1001/jama.2023.19574.

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STRUCTURED ABSTRACT

Question: Are glucagon-like peptide 1 (GLP-1) receptor agonists associated with an increased risk of biliary disease, pancreatitis, and other gastrointestinal (GI) adverse events?

Design: Retrospective cohort study.

Setting: Random sample of 16 million patients (2006-2020) from the PharMetrics Plus database (IQVIA), which is a large health claims database of outpatient prescriptions and *International Classification of Diseases – 9th* and *10th Edition* (*ICD-9/ICD-10*) diagnoses.

Patients and Interventions/Exposure: New users of semaglutide (n= 613) and liraglutide (n=4,144), which are GLP-1 receptor agonists approved for diabetes, and users of buproprion-naltrexone (n= 654), an Federal Drug Administration (FDA)-approved weight loss agent, which served as active comparator.

Outcome: Patients were observed from first prescription of medication to diagnosis of defined GI adverse events, based on *ICD-9/ICD-10* codes or end of the study period in 2020. Biliary disease included cholecystitis, cholelithiasis, and choledocholithiasis. Other GI adverse events of interest were pancreatitis, bowel obstruction, or gastroparesis defined by *ICD-9/ICD-10* coding or use of promotility agent.

Data Analysis: Hazard ratios (HR) calculated using Cox proportional hazards model after adjusting for age, sex, smoking, hyperlipidemia, geographic location, and abdominal surgery in the previous 30 days.

Funding: No funding is reported.

Results: Incidence rates for pancreatitis (adjusted HR [aHR] 9.1, 95% confidence interval [CI] 1.25-66), bowel obstruction (aHR 4.2, 95% CI 1.02-17.4), and gastroparesis (aHR 3.7, 95% CI 1.2-11.9) were significantly higher among users of GLP-1 receptor agonists compared to bupropion-naltrexone users. Biliary disease was numerically higher, but did not achieve statistical significance in the primary analysis: aHR = 1.5; 95% CI: 0.9-2.5.

COMMENTARY

Why Is This Important?

We selected this study, which was published as a Research Letter in *JAMA Medicine*, because it was publicized extensively in the media. As discussed in prior summaries[1], the methodology of these epidemiologic reports is frequently flawed and does not confirm or even support a causal relationship between medicine and adverse event.

Nevertheless, given the popularity of GLP-1 receptor agonists for weight loss and their possible impact on delaying GI motility, gastroenterologists may frequently be asked about potential GI risks of these medications. Notably, although there was not a statistically significant increase in biliary disease among GLP-1 receptor agonist users in this study, the FDA[2] added warnings and precautions about acute cholecystitis and biliary disease to the label in late 2022 based on data from placebo-controlled RCTs as well as other observational data[3].

Key Study Findings

Incidence rates for pancreatitis (aHR 9.1, 95% CI 1.25-66), bowel obstruction (aHR 4.2, 95% CI 1.02-17.4), and gastroparesis (aHR 3.7, 95% CI 1.2-11.9) were significantly higher among users of GLP-1 agonists compared to bupropion-naltrexone users.

Biliary disease was numerically higher,

but did not achieve statistical significance in the primary analysis (aHR 1.5, 95% CI: 0.9-2.5).

Caution

This is a hypothesis-generating study and should not be considered a study that answers a question. Since semaglutide was not approved for weight-loss until 2021 and liraglutide is still only FDA-approved for diabetes, the vast majority of GLP-1 receptor agonist users in this study had diabetes, which may cause gastroparesis. Misclassification frequently occurs with *ICD-9/ICD-10* coding. Furthermore, data on duration and dose of GLP-1 agonist use was not considered.

My Practice

Gastroenterologists frequently see patients with GI symptoms after starting GLP-1 receptor agonists. Since one of us (S.P.) frequently prescribes GLP-1 receptor agonists for metabolic dysfunction-associated fatty liver disease (MAFLD) patients with obesity, a review of some pearls may be helpful.

If these patients have been successful with weight loss and glycemic control of their diabetes, then they may be hesitant to discontinue GLP-1 receptor agonists even if they are suffering from nausea, constipation, or abdominal discomfort—which are common given the medications possible mechanism of action on slowing GI motility. When I prescribe GLP-1 receptor agonists, I gradually increase the dose based on tolerability. Therefore, if a patient develops nausea, then I may revert to a lower dose. If patients develop constipation, then I usually treat with an osmotic laxative without lowering the dose.

I educate my patients that there does appear to be a small risk of developing pancreatitis based on all available data. Also, I explain that significant weight loss does increase the risk of gallstone development and may be associated with increased risk of cholecystitis and choledocholithiasis. This is most likely a result of GLP-1 receptor agonists producing the desired effect, weight loss, as opposed to a direct effect of GLP-1 receptor agonists on reduced gallbladder emptying or suppression of cholecystokinin, which has been hypothesized.[2] Current data is insufficient to support a causal link between GLP-1 receptor agonists and gastroparesis or bowel obstruction.[4-5] Ultimately, discontinuation of GLP-1 receptor agonists usually resolves nausea and vomiting. If the patient is subsequently diagnosed with gastroparesis, it is almost certainly due to underlying diabetes.

The current controversy is whether or not GLP-1 receptor agonists need to be discontinued prior to endoscopic procedures to minimize aspiration risk during monitored anesthesia care. The American Society for Anesthesiology updated their pre-operative fasting guidelines in 2023 and recommended that GLP-1 receptor agonists should be held for 1 week, despite lacking data.[6] Therefore, regardless of the position statements from our GI societies,[7-8] your anesthesiology team may refuse to provide

monitored anesthesia care unless the patient holds their GLP-1 receptor agonist. Since these medications are administered subcutaneous weekly, many patients may forget, leading to a last-minute cancellation of the procedure. In my own practice (P.S.), I do not routinely hold GLP-1 receptor agonists when performing colonoscopy or even upper endoscopy with midazolam and fentanyl for sedation.

For Future Research

Additional studies assessing the impact of GLP-1 receptor agonists on gastric emptying and their potential impact on fasting prior to endoscopic procedures are sorely needed.

Conflict of Interest

Dr. Schoenfeld and Dr. Paul have no relevant conflicts of interest.

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