RESEARCH LETTER

Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Glucagon-like peptide 1 (GLP-1) agonists are medications approved for treatment of diabetes that recently have also been used off label for weight loss.[1] Studies have found increased risks of gastrointestinal adverse events (biliary disease,[2] pancreatitis,[3] bowel obstruction,[4] and gastroparesis[5]) in patients with diabetes.[2-5] Because such patients have higher baseline risk for gastrointestinal adverse events, risk in patients taking these drugs for other indications may differ. Randomized trials examining efficacy of GLP-1 agonists for weight loss were not designed to capture these events[2] due to small sample sizes and short follow-up. We examined gastrointestinal adverse events associated with GLP-1 agonists used for weight loss in a clinical setting.

Supplemental content

Methods | We used a random sample of 16 million patients (2006-2020) from the PharMetrics Plus database (IQVIA), a large health claims database that captures 93% of all outpatient prescriptions and physician diagnoses in the US through the *International Classification of Diseases, Ninth Revision (ICD-9)* or *ICD-10*. In our cohort study, we included new users of semaglutide or liraglutide, 2 main GLP-1 agonists, and the active comparator bupropion-naltrexone, a weight loss agent unrelated to GLP-1 agonists. Because semaglutide was marketed for weight loss after the study period (2021), we ensured all GLP-1 agonist and bupropion-naltrexone users had an obesity code in the 90 days prior or up to 30 days after cohort entry, excluding those with a diabetes or antidiabetic drug code.

Patients were observed from first prescription of a study drug to first mutually exclusive incidence (defined as first *ICD-9* or *ICD-10* code) of biliary disease (including cholecystitis, cholelithiasis, and choledocholithiasis), pancreatitis (including gallstone pancreatitis), bowel obstruction, or gastroparesis (defined as use of a code or a promotility agent). They were followed up to the end of the study period (June 2020) or censored during a switch. Hazard ratios (HRs) from a Cox model were adjusted for age, sex, alcohol use, smoking, hyperlipidemia, abdominal surgery in the previous 30 days, and geographic location, which were identified as common cause variables or risk factors.[6] Two sensitivity analyses were undertaken, one excluding hyperlipidemia (because more semaglutide users had hyperlipidemia) and another including patients without diabetes regardless of having an obesity code. Due to absence of data on body mass index (BMI), the E-value was used to examine how strong unmeasured confounding would need to be to negate observed results, with

Table 1. Characteristics of Semaglutide, Liraglutide, and Bupropion-Naltrexone Users

	Semaglutide	Liraglutide	Bupropion-naltrexone
No.	613	4144	654
Age, mean (SD), y	53.5 (11.9)	51.3 (12.2)	45.2 (11.1)
Sex, %			
Male	55.8	61.0	82.4
Female	44.2	39.0	17.6
Follow-up, median (IQR), y	0.6 (0.2-1.1)	1.7 (0.8-3.1)	1.7 (0.7-2.9)
Covariates, %			
Alcohol[a]	2.9	0.4	0.6
Smoking[a]	8.7	12.5	9.9
Hyperlipidemia[b]	55.6	22.8	11.5
Abdominal surgery[c]	0	0.12	0
US region			
Northeast	18.3	25.8	18.3
Southeast	34.6	26.1	34.6
Midwest	33.1	30.3	33.1
Southwest	0.2	2.6	0.3
West	13.9	15.3	12.4
Incidence (No.)[d]			
Biliary disease	11.7 (5)	18.6 (162)	12.6 (16)
Pancreatitis	4.6 (2)	7.9 (71)	1.0 (1)
Bowel obstruction	0	8.1 (73)	1.7 (2)
Gastroparesis	9.1 (4)	7.3 (66)	3.1 (3)

[a] Alcohol and smoking were defined as any codes for alcohol use or smoking in 1 year prior to cohort entry.

[b] Hyperlipidemia was defined as any code for hyperlipidemia or dyslipidemia in 1 year prior to cohort entry.

[c] Any abdominal surgery in previous 30 days.

[d] Incidence per 1000 person-years.

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

Outcomes	GLP-1 agonists, HR (95% CI)[a]		Bupropion-naltrexone
	Crude	Adjusted[b]	
Primary analysis			
Biliary disease	1.48 (0.88-2.47)	1.50 (0.89-2.53)	1 [Reference]
Pancreatitis	10.33 (1.44-74.40)	9.09 (1.25-66.00)	1 [Reference]
Bowel obstruction	5.16 (1.27-21.00)	4.22 (1.02-17.40)	1 [Reference]
Gastroparesis	3.31 (1.04-10.50)	3.67 (1.15-11.90)	1 [Reference]
Sensitivity analyses			
Exclusion of hyperlipidemia			
Biliary disease	1.50 (0.88-2.56)	1.46 (0.84-2.51)	1 [Reference]
Pancreatitis	9.80 (1.36-70.79)	7.99 (1.10-58.30)	1 [Reference]
Bowel obstruction	4.43 (1.08-18.20)	3.63 (0.87-15.10)	1 [Reference]
Gastroparesis	3.32 (1.04-10.60)	3.67 (1.14-11.80)	1 [Reference]
Analysis with less-restrictive obesity definition[c]			
Biliary disease	1.29 (0.92-1.80)	1.20 (0.85-1.69)	1 [Reference]
Pancreatitis	6.19 (1.99-19.30)	5.94 (1.90-18.60)	1 [Reference]
Bowel obstruction	3.11 (1.28-7.54)	2.44 (1.00-5.95)	1 [Reference]
Gastroparesis	2.11 (1.09-4.09)	2.35 (1.20-4.58)	1 [Reference]
E-values for adjusted HRs[d]			
Biliary disease	2.36		
Pancreatitis	17.67		
Bowel obstruction	7.91		
Gastroparesis	6.80		

Abbreviations: GLP-1, glucagon-like peptide 1; HR, hazard ratio.

[a] Either semaglutide or liraglutide user.

[b] Hazard ratios adjusted for by age, sex, alcohol use, smoking, hyperlipidemia, and abdominal surgery in the last 30 days.

[c] Analysis that included patients without a diabetes code with or without an obesity code.

[d] E-values represent the HRs for the association of an unmeasured confounder (in this study's case, body mass index) with GLP-1 agonists and the study's 4 outcomes. E-values with HRs at least 2 suggest that such confounders are unlikely to change study results.

E-value HRs of at least 2 indicating BMI is unlikely to change study results. Statistical significance was defined as 2-sided 95% CI that did not cross 1. Analyses were performed using SAS version 9.4. Ethics approval was obtained by the University of British Columbia's clinical research ethics board with a waiver of informed consent.

Results | Our cohort included 4144 liraglutide, 613 semaglutide, and 654 bupropion-naltrexone users. Incidence rates for the 4 outcomes were elevated among GLP-1 agonists compared with bupropion-naltrexone users (**Table 1**). For example, incidence of biliary disease (per 1000 person-years) was 11.7 for semaglutide, 18.6 for liraglutide, and 12.6 for bupropion-naltrexone and 4.6, 7.9, and 1.0, respectively, for pancreatitis.

Use of GLP-1 agonists compared with bupropion-naltrexone was associated with increased risk of pancreatitis (adjusted HR, 9.09 [95% CI, 1.25-66.00]), bowel obstruction (HR, 4.22 [95% CI, 1.02-17.40]), and gastroparesis (HR, 3.67 [95% CI, 1.15-11.90) but not biliary disease (HR, 1.50 [95% CI, 0.89-2.53]). Exclusion of hyperlipidemia from the analysis did not change the results (**Table 2**). Inclusion of GLP-1 agonists regardless of history of obesity reduced HRs and narrowed CIs but did not change the significance of the results (Table 2). E-value HRs did not suggest potential confounding by BMI.

Discussion | This study found that use of GLP-1 agonists for weight loss compared with use of bupropion-naltrexone was associated with increased risk of pancreatitis, gastroparesis, and bowel obstruction but not biliary disease.

Given the wide use of these drugs, these adverse events, although rare, must be considered by patients who are contemplating using the drugs for weight loss because the risk-benefit calculus for this group might differ from that of those who use them for diabetes. Limitations include that although all GLP-1 agonist users had a record for obesity without diabetes, whether GLP-1 agonists were all used for weight loss is uncertain.

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1. Sauer N, Reining F, Schulze Zur Wiesch C, Burkhardt T, Aberle J. Off-label antiobesity treatment in patients without diabetes with GLP-1 agonists in clinical practice. *Horm Metab Res*. 2015;47(8):560-564.

2. Rubino DM, Greenway FL, Khalid U, et al; STEP 8 Investigators. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA*. 2022;327(2):138-150. doi:10.1001/jama.2021.23619

3. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1–based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med*. 2013;173(7):534-539. doi:10.1001/jamainternmed.2013.2720

4. Gudin B, Ladhari C, Robin P, et al. Incretin-based drugs and intestinal obstruction: a pharmacovigilance study. *Therapie*. 2020;75(6):641-647. doi:10.1016/j.therap.2020.02.024

5. Kalas MA, Galura GM, McCallum RW. Medication-induced gastroparesis: a case report. *J Investig Med High Impact Case Rep*. 2021;9:23247096211051919.

6. Etminan M, Collins GS, Mansournia MA. Using causal diagrams to improve the design and interpretation of medical research. *Chest*. 2020;158(1S):S21-S28. doi:10.1016/j.chest.2020.03.011