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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 for Academics 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 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

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

	GLP-1 agonists, HR (95% CI)[a]		
Outcomes	Crude	Adjusted[b]	Bupropion-naltrexone
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.

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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US Medical Student Plans to Practice in Underserved Areas

Unequal access to health care contributes to health disparities.[1,2] A suggested approach to improving access to care is to increase the diversity of the workforce[1,2] because minority physicians disproportionally practice in underserved areas.

Supplemental content

Studies conducted before 2013 reported racial and ethnic minority medical students were more likely to primarily intend to care for underserved populations.[3,4] No recent study has explored medical students' intent to practice in underserved areas, and previous analyses combined racial and ethnic identities and did not include sexual orientation or an intersectional lens.[3,5,6] We analyzed medical students' intent to practice in underserved areas from 2019 to 2021 by demographic characteristics.

Methods | The Association of American Medical Colleges (AAMC) administers a web-based questionnaire to individuals graduating from an allopathic US medical school. The AAMC linked survey responses from 2019, 2020, and 2021 to AAMC sources that included demographic factors previously provided by responders. We obtained a deidentified data set that included demographics and response to the item "Do you plan to work primarily in an underserved area?" Medical schools without all 3 years of data were excluded. The study was deemed exempt by the Mayo Clinic and University of Colorado institutional review boards.

Responses were pooled across years. Analysis included summary statistics, χ^2 tests, and a logistic regression model for intent to practice in an underserved area that included age at graduation, race, ethnicity, sexual orientation, and debt (premedical school, medical school, and consumer). All tests were 2-sided, with a type I error of .05. All comparisons were performed using SAS version 9.4 (SAS Institute).

Results | The total number of respondents was 48 885 (response rate, 80.7%) from 139 (of 148) medical schools. Of these, 45 687 (93.4%) answered the item about intent to practice in an underserved area (**Table**). Among the latter cohort, 51.4% were women, 8.1% were Hispanic, 63.9% were White, and 91.9% were heterosexual. Overall, 27.6% indicated they planned to work primarily in an underserved area. Considering demographics, 33.1% of female, 46.2% of American Indian or Alaska Native, 54.9% of Black or African American, 43.6% of Hispanic, 37.5% of Native Hawaiian or Other Pacific Islander, and 43.6% of bisexual students intended to practice in an underserved area. After controlling for other factors, women had higher odds of intent to practice in an underserved area than men (odds ratio [OR], 1.80; 95% CI, 1.72-1.88) (Table). American Indian or Alaska Native (OR, 1.82; 95% CI, 1.44-2.29); Black or African American (OR, 2.09; 95% CI, 1.87-2.33); Hispanic, Latino, or of Spanish origin (OR, 1.71; 95% CI, 1.56-1.86); and Native Hawaiian or Other Pacific Islander (OR, 1.65; 95% CI, 1.14-2.39) students had higher odds of intent to practice in an underserved area than those who did not identify with each of those respective racial and ethnic groups. Bisexual (OR, 1.86; 95% CI, 1.67-2.06) or