

Delayed Gastric Emptying More Likely, Gallstones and Ileus Less Likely for Diabetic Patients on GLP-1 Medications Compared to Diabetics on Other Treatments

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Key Findings:

- Diabetic patients prescribed four of the five glucagon-like peptide-1 receptor agonist (GLP-1) medications studied experienced increased likelihood of delayed gastric emptying (gastroparesis) compared to those not on a GLP-1 medication.
- Diabetic patients prescribed GLP-1 medications are less likely to be diagnosed with gallstones or ileus compared to diabetic patients not on GLP-1 medications.

Gastrointestinal (GI) side effects including delayed gastric emptying, gallstones, and ileus have been associated with glucagon-like peptide-1 receptor agonist (GLP-1) medications.^{1,2} The U.S. Food & Drug Administration (FDA) required a safety label for Ozempic (semaglutide) warning of the potential risk of ileus, a condition characterized by impaired intestinal motility.^{3,4}

To further understand the correlation between GLP-1 medications and GI side effects, we studied 12 million diabetic patients, including 4.6 million on GLP-1 medications and 7.4 million not on GLP-1 medications. We wanted to increase the likelihood that we were studying only patients who were being actively managed. For the patients on GLP-1 medications, that prescription served as adequate evidence. For patients not on GLP-1 medications, we included only those who had a completed HbA1c test. We adjusted for patient sex, age, social vulnerability, BMI classification, race, ethnicity, and insulin usage.

We found that delayed gastric emptying (gastroparesis) was more likely for diabetic patients on most GLP-1 medications studied compared to diabetics not on GLP-1 medications. Patients on exenatide had the greatest increase in likelihood of this condition (135%), while those on tirzepatide had a 29% reduction in likelihood. Gallstones and ileus were less likely for patients prescribed most of the GLP-1 medications studied compared to diabetic patients not prescribed a GLP-1 medication. Patients on semaglutide had a 22% reduced likelihood of gallstones while those on tirzepatide did not experience a statistically significant change in the likelihood. For ileus, tirzepatide had the greatest reduction in likelihood (62%) while exenatide had the lowest reduction (43%).

GI Side Effect Likelihood by GLP-1 Medication Among Diabetic Patients

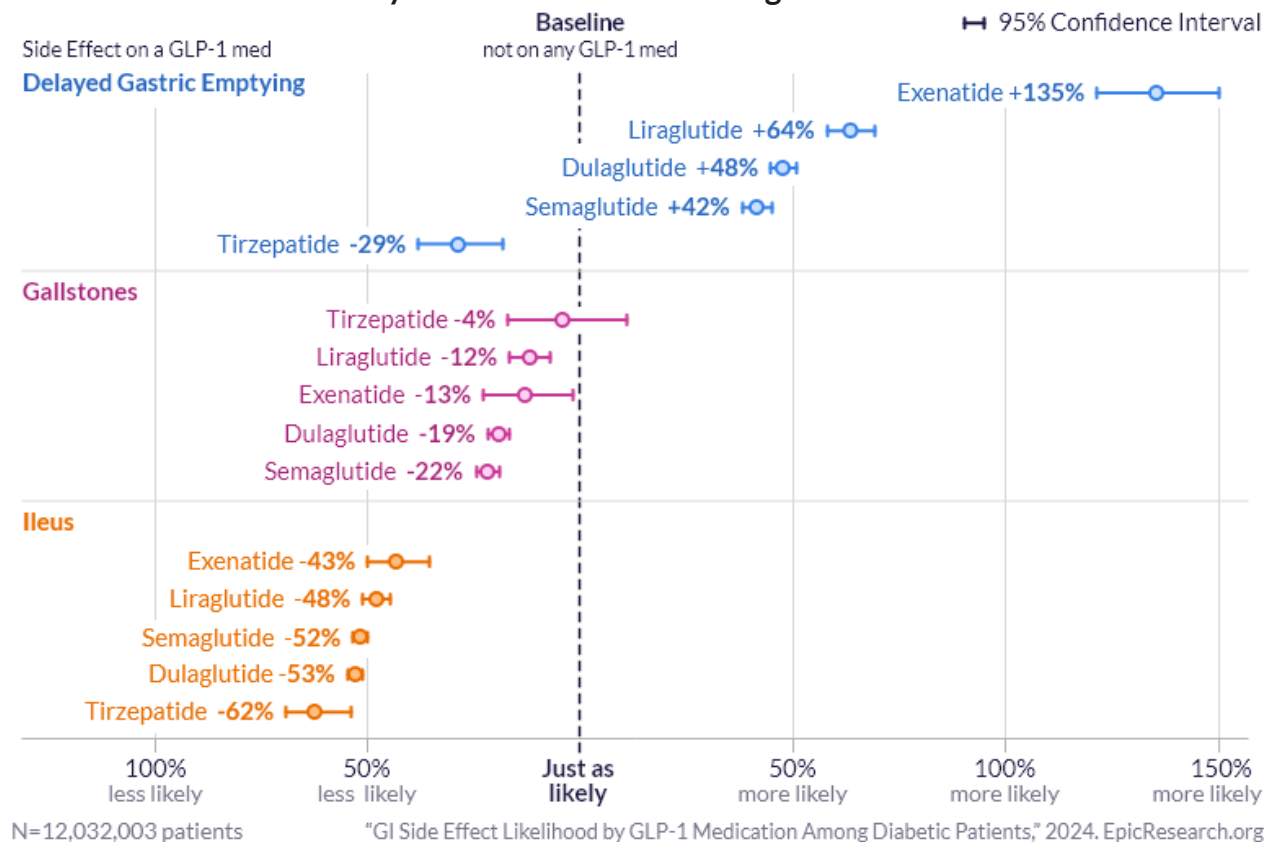


Figure 1. The likelihood of diabetic patients being diagnosed with a GI side effect after a GLP-1 prescription.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 246 million patient records from 1,400 hospitals and more than 32,800 clinics from all 50 states and Lebanon. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

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3. Drug safety-related labeling changes (SrLC). U.S. Food and Drug Administration. <https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2183>. Accessed January 17, 2024.
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Data Definitions

Term	Definition
Study period	1/1/2017 to 9/1/2023
Study population	Patients with an index event between 1/1/2017 and 3/1/2023. Excluded patients with any of the outcomes before their index event.
Case population	A diabetes diagnosis and a medication order for a GLP-1 medication.
Control populations	Patients with an HbA1c lab result.
Index event	Date of the medication order or HbA1c result for the diabetic control population.
Outcomes	A diagnosis or delayed gastric emptying, ileus, or gallstones between 14 and 180 days following beginning of treatment.
Delayed gastric emptying	A diagnosis with ICD-10-CM code K31.84.
Ileus	A diagnosis with ICD-10-CM code K56.0 or K56.7.
Gallstones	A diagnosis with ICD-10-CM code K81.
Obesity class	Not Obese: BMI <30 Class 1 Obesity: BMI between 30 and 35 Class 2 Obesity: BMI between 35 and 40 Class 3 Obesity: BMI 40+
Diabetes	A diagnosis with SNOMED CT code 44054006.
GLP-1	Any drug with one of the following pharmaceutical classes: ANTI-OBESITY GLUCAGON-LIKE PEPTIDE-1 RECEPT AGONIST ANTIHYPERGLY,INCRETIN MIMETIC(GLP-1 RECEPT.AGONIST) ANTIHYPERGLY,INCRETIN,LONG ACT-GLP-1 RECEPT.AGONIST
GLP-1 drugs of interest	A drug in the GLP-1 group with a simple generic name like: Semaglutide Liraglutide Dulaglutide Exenatide Tirzepatide
Insulin	Drugs with a pharmaceutical class of INSULINS.
HbA1c lab	A lab with LOINC code 17856-6, 17855-8, 41995-2, 4548-4, 4549-2, or 55454-3.

Table 1. GI Side Effect Likelihood by GLP-1 Medication Among Diabetic Patients – Delayed Gastric Emptying

	Odds Ratio	Lower CI	Upper CI
semaglutide	1.416	1.382	1.451
liraglutide	1.637	1.583	1.694
tirzepatide	0.713	0.620	0.820
dulaglutide	1.477	1.445	1.510
exenatide	2.353	2.212	2.503
Insulin	5.346	4.967	5.754

Male	0.699	0.687	0.711
Age	0.981	0.980	0.981
SVI	1.593	1.544	1.642
BMI Class 2 Obesity	0.844	0.821	0.868
BMI Class 3 Obesity	0.825	0.803	0.847
BMI Not Obese	1.167	1.141	1.194
BMI Unknown	0.830	0.804	0.858
Asian	0.572	0.528	0.619
Black	0.930	0.910	0.949
Hispanic	0.838	0.815	0.862

Table 2. GI Side Effect Likelihood by GLP-1 Medication Among Diabetic Patients – Gallstones

	Odds Ratio	Lower CI	Upper CI
semaglutide	0.783	0.756	0.812
liraglutide	0.881	0.833	0.931
tirzepatide	0.958	0.829	1.108
dulaglutide	0.809	0.783	0.835
exenatide	0.870	0.771	0.982
Insulin	2.082	1.957	2.215
Male	1.059	1.035	1.084
Age	1.015	1.014	1.016
SVI	0.972	0.933	1.013
BMI Class 2 Obesity	1.146	1.106	1.187
BMI Class 3 Obesity	1.061	1.023	1.100
BMI Not Obese	0.903	0.875	0.931
BMI Unknown	0.832	0.797	0.869
Asian	0.961	0.881	1.048
Black	0.820	0.795	0.846
Hispanic	0.911	0.873	0.951

Table 3. GI Side Effect Likelihood by GLP-1 Medication Among Diabetic Patients – Ileus

	Odds Ratio	Lower CI	Upper CI
semaglutide	0.482	0.464	0.501
liraglutide	0.521	0.490	0.554
tirzepatide	0.376	0.307	0.462
dulaglutide	0.470	0.454	0.487

exenatide	0.569	0.500	0.647
Insulin	3.225	3.008	3.457
Male	1.510	1.477	1.542
Age	1.015	1.015	1.016
SVI	1.355	1.305	1.407
BMI Class 2 Obesity	1.095	1.057	1.135
BMI Class 3 Obesity	1.370	1.324	1.418
BMI Not Obese	1.276	1.240	1.312
BMI Unknown	0.695	0.664	0.728
Asian	1.533	1.436	1.636
Black	1.026	0.999	1.054
Hispanic	0.807	0.774	0.841