Most GLP-1 Medications Correlated with a Lower Likelihood of Anxiety and Depression Diagnoses

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Key Findings:

- Diabetic patients prescribed tirzepatide, semaglutide, dulaglutide, and exenatide are less likely to be diagnosed with depression after starting the medication compared to those not on a glucagon-like peptide-1 receptor agonist (GLP-1) medication.
- The likelihood of anxiety in diabetic patients is lower for those on all five GLP-1 medications studied.
- Among non-diabetic patients, semaglutide is correlated with a lower likelihood of depression and anxiety, while liraglutide showed no statistically significant difference compared to those on non-GLP-1 weight management medications.

Glucagon-like peptide-1 receptor agonist (GLP-1) medications have been used for glucose control in diabetic patients for several years. Recently, the U.S. Food and Drug Administration (FDA) approved some GLP-1 medications, including semaglutide and liraglutide, for weight management in obese patients.[1] Notably, one such medication, Wegovy, which has a main active ingredient of semaglutide, lists depression and suicidal ideation as potential side effects.[2] Other GLP-1 medications, including another with semaglutide as a main active ingredient, do not list depression or suicidal ideation as potential side effects.[3] An initial evaluation by the FDA suggests no direct link between GLP-1 medications and suicidal ideation.[1]

To better understand the potential relationship between GLP-1 medications and mental health diagnoses after starting the medications, we studied 3,081,254 diabetic patients and 929,174 non-diabetic patients. We adjusted for patient age, sex, and history of depression or anxiety. For the diabetic population, we also adjusted for HbA1c level and use of other diabetic medications. For the non-diabetic population, we adjusted for BMI classification. For the diabetic population, we compared patients prescribed GLP-1 medications to patients with an HbA1c level documented. For the non-diabetic population, we compared patients prescribed GLP-1 medications to patients prescribed a non-GLP-1 weight management medication.

We first investigated the correlation between GLP-1 medications and depression diagnosis after starting the medication. Among diabetic patients, those prescribed any of the GLP-1 medications studied, except for liraglutide, showed a decreased likelihood of depression compared to those not prescribed the GLP-1 medication. Tirzepatide showed the greatest reduction in likelihood of depression for diabetic patients (65%), as shown in Figure 1. Among non-diabetic patients, those prescribed semaglutide had a lower likelihood of depression compared to those not prescribed the GLP-1 medication. Liraglutide showed no statistically significant difference in depression diagnoses for non-diabetic patients.

Depression Likelihood by GLP-1 Medication

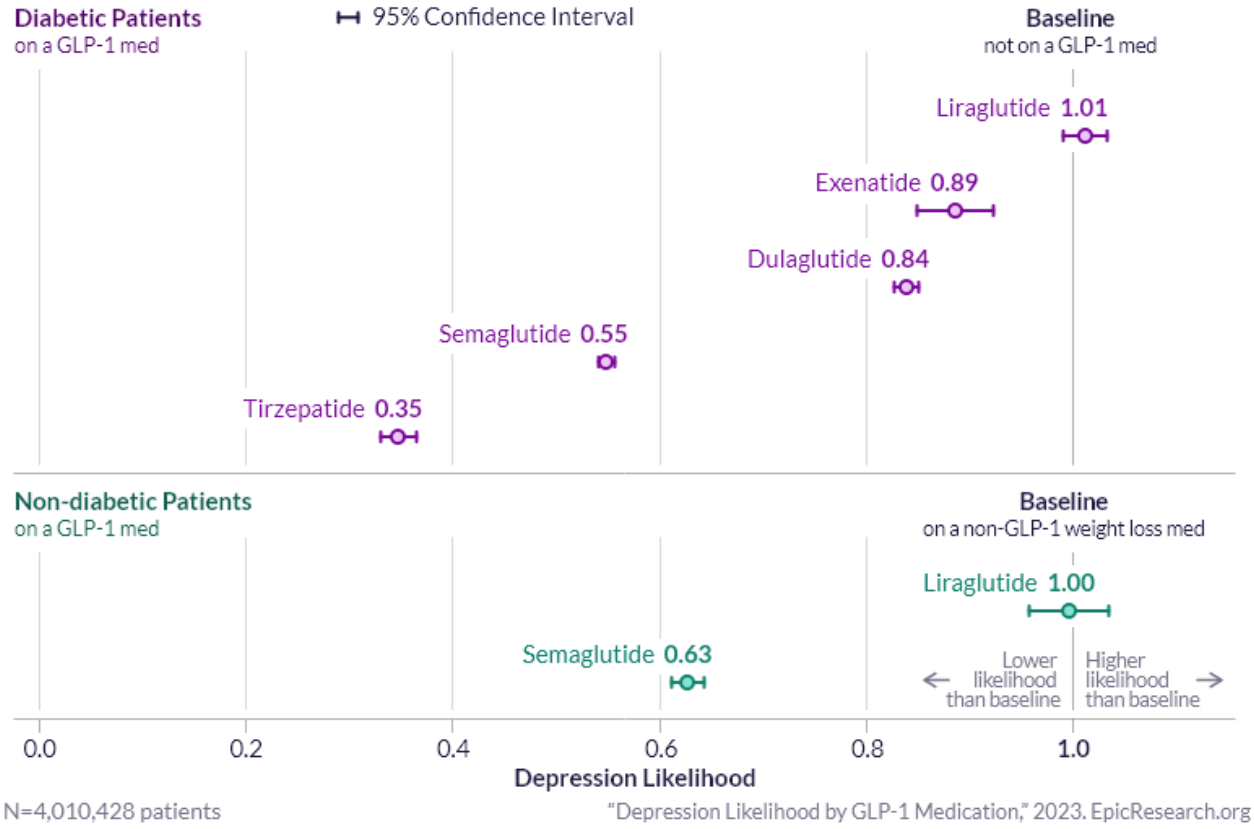

Figure 1. The likelihood of patients being diagnosed with depression after a GLP-1 prescription compared to those on a non-GLP-1 medication.

Next, we evaluated the relationship between GLP-1 medications and anxiety. Similar to depression, diabetic patients prescribed any of the GLP-1 medications had a lower likelihood of being diagnosed with anxiety after starting the medication compared to those not prescribed a GLP-1 medication. Tirzepatide showed the greatest reduction in likelihood, with a 60% reduction, as seen in Figure 2. Among non-diabetic patients, only those prescribed semaglutide had a lower likelihood of anxiety compared to those not prescribed the GLP-1 medication, while those prescribed liraglutide had no statistically significant difference.

Anxiety Likelihood by GLP-1 Medication

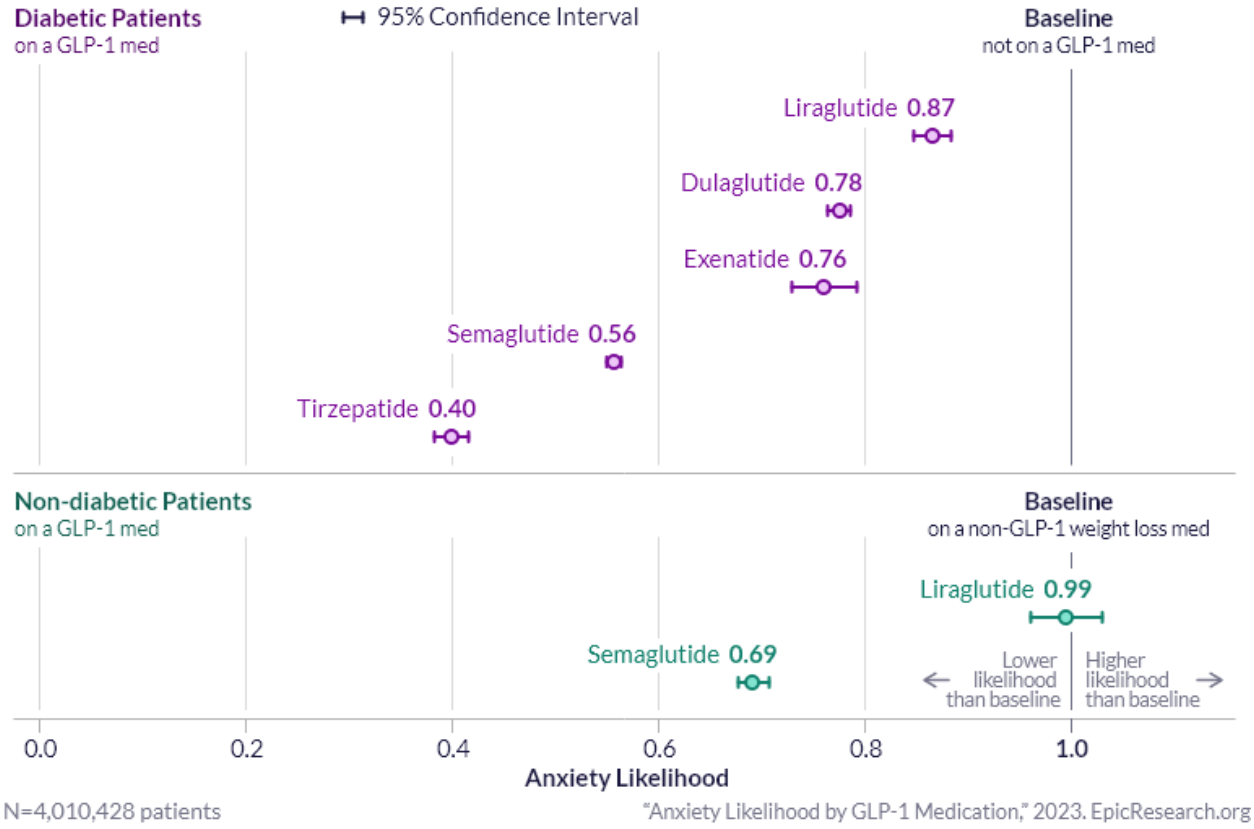

Figure 2. The likelihood of patients being diagnosed with anxiety after a GLP-1 prescription compared to those on a non-GLP-1 medication.

These data come from Cosmos, a collaboration of Epic health systems representing more than 233 million patient records from 1,325 hospitals and more than 28,900 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

1. Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity. U.S. Food and Drug Administration. Published January 11, 2024. https://www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type. Accessed January 16, 2024.
2. Common Side Effects of Wegovy®. Wegovy. https://www.wegovy.com/taking-wegovy/side-effects.html. Accessed January 16, 2024.
3. Possible Side Effects of Ozempic® (semaglutide) Injection. Ozempic. https://www.ozempic.com/how-to-take/side-effects.html. Accessed January 26, 2024.

Data Definitions

Term	Definition
Study period	1/1/2017 – 6/1/2023
Study population	*Index Date:* Date of **GLP-1 medication** order *Censorship Date:* 1 year following index date, patient death date, or day of last outpatient encounter (whichever comes first). *End Date:* 1 month after completion of **GLP-1**, or censorship date (whichever comes first). Common Cohort definitions: • Patients with their first ever recorded **GLP-1** prescription. • Patients with **continuous GLP-1 usage** for 60 days. • Patients who have at least 60 days between their **GLP-1** start date and censorship date, unless they died. ○ Patients who died within 60 days are included in the study and censored at their death date. • Patients who have a male or female sex documented. • Patients who have an **SVI** recorded. Non-Diabetic Cohort: • Patients without a diabetes diagnosis within 1 year of or any time before treatment with a GLP-1. • Patients with a documented starting BMI that is greater than or equal to 30 in the year prior to, or up to 30 days following, the start of the semaglutide or liraglutide. Diabetic Cohort: • Patients with a **diabetes** diagnosis prior to, or within 30 days of, starting treatment. Patients with an **uncertain treatment** regimen were excluded.
Control populations	Non-Diabetic Cohorts: • Patients taking ***other weight management drugs.*** Diabetic Cohort: • Patients with a randomly selected **HbA1c** lab results following their diabetes diagnosis.
Other weight management drugs	Orders with one of the following pharmaceutical classes and not associated with any **GLP-1** simple generics: • ANTI-OBESITY SEROTONIN 2C RECEPTOR AGONISTS • ANTI-OBESITY-OPIOID ANTAG-NOREPI,DOPAMINE RU INHIB • ANTI-OBESITY – ANOREXIC AGENTS • ANTI-OBESITY – MELANOCORTIN 4 RECEPTOR AGONISTS
Other HbA1c management drugs	Drugs with one of the following pharmaceutical classes and not associated with any **GLP-1** simple generics: • ANTIHYPERGLYCEMIC, DPP-4 INHIBITORS • ANTIHYPERGLYCEMIC, DPP-4 INHIBITOR-BIGUANIDE COMBS. • ANTIHYPERGLY-SGLY-2 INHIB, DPP-4 INHIB,BIGUANIDE CB

	• ANTIHYPERGLYCEMIC, SGLT-2 AND DPP-4 INHIBITOR COMB • ANTIHYPERGLYCEMIC, BIGUANIDE TYPE • ANTIHYPERGLYCEMIC, BIGUANIDE DIETARY SUPPL. COMB. • ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE AND BIGUANIDE • ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.-BIGUANIDE • ANTIHYPERGLYCEMIC-SOD/GLUC CONTRANSPORT2(SGLT2) INH • ANTIHYPERGLYCEMIC-SGLT2 INHIBITOR-BIGUANIDE COMBS. • ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE • ANTIHYPERGLYCEMIC, THIAZILIDINEDIONE-SULFONYLUREA • ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE(PPARG AGONIST)
Continuous GLP-1 usage	We use the number of refills listed on the order to calculate the approximate end date of the medication. Refill Formula derived from UpToDate information about prescription habits of each **GLP-1,** verified by analyzing the average time between subsequent GLP-1 orders in Cosmos. • Days of treatment ((# of Refills + 1) * 28)
Estimated end of treatment date	Calculated the date following the last end date of a contiguous period of **GLP-1** treatment represented by the End Date calculated based on the number of refills as (refills + 1) * 28 after the treatment start date.
Pre-treatment BMI	Patient's most recent BMI recorded within the 1 year prior to and 30 days following start of GLP-1 treatment
HbA1c lab	A lab with LOINC code 17856-6, 17855-8, 41995-2, 4548-4, 4549-2, 55454-3.
GLP-1 medications	Any drug with one of the following pharmaceutical classes: ANTI-OBESITY GLUCAGON-LIKE PEPTIDE-1 RECEP AGONIST ANTIHYPERGLY,INCRETIN MIMETIC(GLP-1 RECEP.AGONIST) ANTIHYPERGLY,INCRETIN,LONG ACT-GLP-1 RECEPT.AGONIST
GLP-1 medications of interest	Within the **GLP-1** group, any drug with a simple generic name like: • Semaglutide • Liraglutide • Dulaglutide • Exenatide • Tirzepatide
Uncertain treatment	If two or more different **GLP-1 RA** medications are prescribed one after another or the dosage doesn't match an expected dosage, the treatment period is indicated as "Unsure".
Obesity classification	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 ICD-10-CM code E11*.
Depression	A diagnosis with ICD-10-CM code F32.*, F33.*, F06.31*, F06.32*, or F34.1*.
Anxiety	A diagnosis with ICD-10-CM code F40.*, F41.*, F06.4*, F93.0*, or F94.0*.

Table 1: Depression Likelihood by GLP-1 Medication

GLP-1 Medication (Population)	Odds Ratio	Lower 95% CI	Upper 95% CI
Liraglutide (Diabetic)	1.01	0.99	1.03
Exenatide (Diabetic)	0.89	0.85	0.92
Dulaglutide (Diabetic)	0.84	0.83	0.85
Semaglutide (Diabetic)	0.55	0.54	0.56
Tirzepatide (Diabetic)	0.35	0.33	0.36
Liraglutide (Non-diabetic)	1.00	0.96	1.04
Semaglutide (Non-diabetic)	0.63	0.61	0.64

Table 2: Anxiety Likelihood by GLP-1 Medication

GLP-1 Medication (Population)	Odds Ratio	Lower 95% CI	Upper 95% CI
Liraglutide (Diabetic)	0.87	0.85	0.88
Dulaglutide (Diabetic)	0.78	0.76	0.79
Exenatide (Diabetic)	0.76	0.73	0.79
Semaglutide (Diabetic)	0.56	0.55	0.56
Tirzepatide (Diabetic)	0.40	0.38	0.42
Liraglutide (Non-diabetic)	0.99	0.96	1.03
Semaglutide (Non-diabetic)	0.69	0.68	0.71