GLP-1 Medications Associated with Reduced Likelihood of Dementia Compared to Other Diabetic Meds

Team A: Kersten Bartelt, RN; Gregory Edwards, PhD
Team B: Christopher Alban, MD; Eric Barkley
Last updated 05 December 2024 • Check for updates at EpicResearch.org

Key Findings:

- Patients with diabetes who are prescribed semaglutide, exenatide, liraglutide, or dulaglutide experience a 23–44% reduced likelihood of dementia compared to those prescribed other diabetes management medications.

There have been reports on the relationship between GLP-1 medications and dementia, with some finding a reduced risk of dementia following a GLP-1 medication prescription[1] and others indicating variability depending on how these medications cross the blood-brain barrier.[2]

To further understand this relationship, we studied 549,822 patients with diabetes aged 60 or older. These patients were prescribed either a GLP-1 medication or another type of diabetes management medication and were observed for a dementia diagnosis within five years of starting the medication. We adjusted for patient age, sex, race, ethnicity, Social Vulnerability Index quintile, starting BMI, weight change after treatment, history of insulin usage, and starting HbA1c. For this study, dementia was defined to include Alzheimer's disease as well as vascular and non-vascular dementias.

We found that patients prescribed semaglutide had a 44% reduced likelihood of a dementia diagnosis compared to those prescribed a non-GLP-1 diabetes management medication, as seen in Figure 1. Similarly, patients prescribed exenatide experienced a 32% reduced likelihood, those prescribed liraglutide had a 27% reduced likelihood, and those prescribed dulaglutide had a 23% reduced likelihood.

Five-Year Likelihood of Dementia Diagnosis by Diabetes Medication

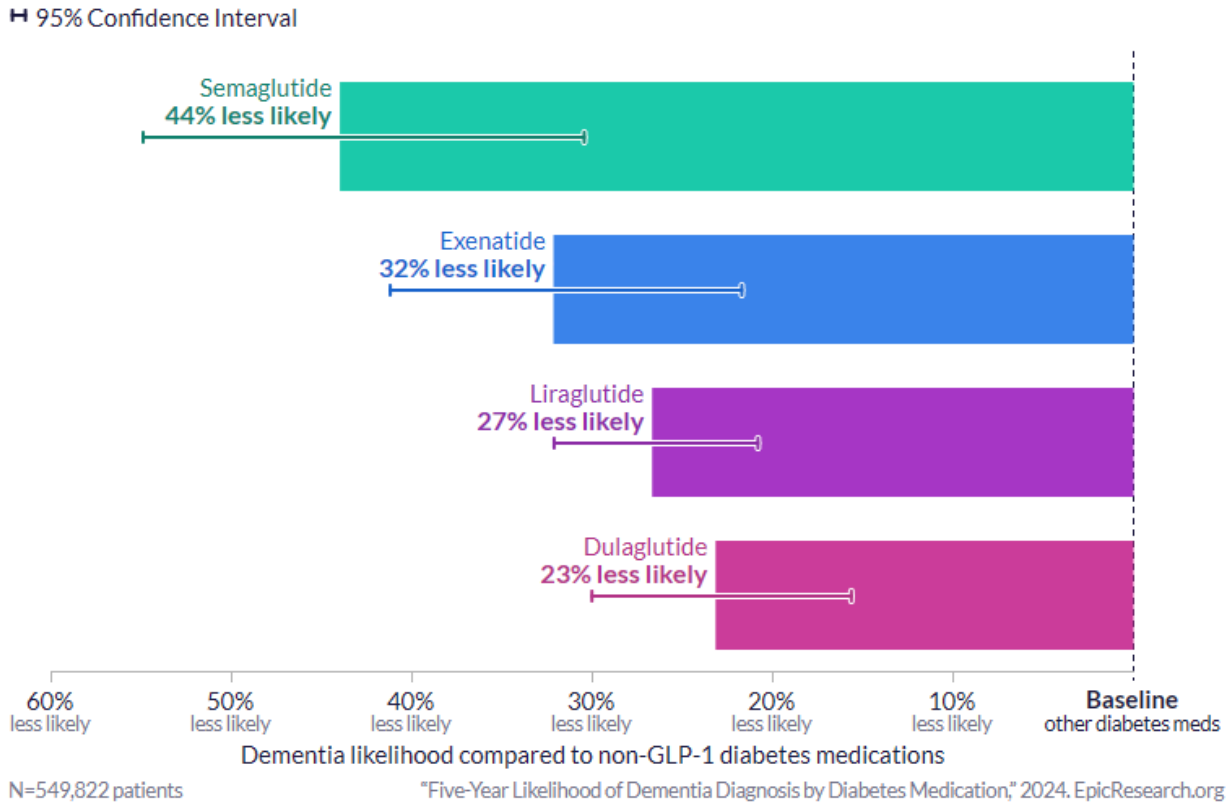

Figure 1. The likelihood of a diabetic patient being diagnosed with dementia within five years by medication.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 277 million patient records from 1,500 hospitals and more than 36,000 clinics from all 50 states, Lebanon, and Saudi Arabia. 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. Tang B, Sjölander A, Wastesson JW, et al. Comparative effectiveness of glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sulfonylureas on the risk of dementia in older individuals with type 2 diabetes in Sweden: an emulated trial study. EClinicalMedicine. 2024;73(102689):102689. doi:10.1016/j.eclinm.2024.102689
2. Fessel J. All GLP-1 agonists should, theoretically, cure Alzheimer's dementia but dulaglutide might be more effective than the others. J Clin Med. 2024;13(13):3729. doi:10.3390/jcm13133729

Data Definitions

Term	Definition
Study period	1/1/2010 to 6/30/2024
Study population	Patients must: • Be aged 60 or older with **type 2 diabetes** and be prescribed a **GLP-1 medication** or a different **diabetes management medication** with no history of a **GLP-1 medication.** • Have at least one outpatient face-to-face encounter within five years prior to their index date.

	• Have five years of follow-up after the index date. • Have an **HbA1c** level and weight within the five years before through three months after the index date. • Have a weight measurement in month nine of treatment or later. Exclusion: • Patients with a history of **dementia** in five years prior to index date
Type 2 diabetes	A diagnosis with ICD-10-CM code E11* or SNOMED CT 44054006
Dementia	Vascular dementia: ICD-10-CM code F01* Non-vascular dementia: ICD-10-CM code F02* or F03* Alzheimer's: ICD-10-CM code G30*
GLP-1 medications	Semaglutide: RxNorm 1991302 Dulaglutide: RxNorm 1551291 Exenatide: RxNorm 60548 Liraglutide: RxNorm 475968
Diabetes management medications	Drugs identified by pharmaceutical classes DPP-4i: ANTIHYPERGLYCEMIC, DPP-4 INHIBITORS; ANTIHYPERGLYCEMIC, DPP-4 INHIBITOR-BIGUANIDE COMBS. Sulfonylurea: ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.- BIGUANIDE; ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE SGLT2i: ANTIHYPERGLYCEMIC-SOD/GLUC COTRANSPORT2(SGLT2) INH; ANTIHYPERGLYCEMIC-SGLT2 INHIBITOR-BIGUANIDE COMBS. DPP-4 Inhibitors + SGLT2: ANTIHYPERGLY-SGLT-2 INHIB,DPP-4 INHIB, BIGUANIDE CB; ANTIHYPERGLYCEMIC, SGLT-2 AND DPP-4 INHIBITOR COMB Thiazolidinedione: ANTIHYPERGLYCEMIC,THIAZOLIDINEDIONE(PPARG AGONIST); ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE-SULFONYLUREA; ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE AND BIGUANIDE Thiazolidinedione + DPP-4i: ANTIHYPERGLY,DPP-4 ENZYME INHIB.-THIAZOLIDINEDIONE
Confounders	Baseline BMI classification: • Underweight: <18.5 • Healthy: 18.5-25 • Overweight: 25-30 • Obese: >30 Weight lost in the first six months of treatment: • Gained at least 5 pounds • Between 5 pounds gained and 5 pounds lost • Lost between 5 and 20 pounds • Lost more than 20 pounds

	Baseline **HbA1c**: • <5.7 • 5.7-6.3 • 6.4-7.9 • 8+ Age at start of treatment: • 60-74 • 75+ RUCA: (Rural or small town) vs. (micropolitan or metropolitan) Legal sex: male/female SVI quintile CVD within the five years prior: ICD-10-CM code I24*-I26*, I30*-I49*, I51*, or I70*-I79* Hypertension within the five years prior: ICD-10-CM code I10*-I16* **Insulin** use within year prior **Metformin** use within year prior **Race and ethnicity**
HbA1c	Lab result associated with one of the following LOINC codes: 17855-8, 17856-6, 41995-2, 4548-4, 4549-2, or 55454-3
Insulin	A medication order with a pharmaceutical class of "INSULINS"
Metformin	A medication order with a pharmaceutical class of "ANTIHYPERGLYCEMIC, BIGUANIDE TYPE" or "ANTIHYPERGLYCEMIC, BIGUANIDE-DIETARY SUPPL. COMB."
Race and ethnicity	Patients were classified by self-identified race and ethnicity that was then mapped to OMOP standards. Patients were classified as Hispanic or non-Hispanic as well as Black or non-Black.
Model specifications	Logistic regression for three-year and five-year outcome Survival analysis as sensitivity analysis for patients lost to follow-up

Table 1: Five-Year Likelihood of Dementia Diagnosis by Diabetes Medication

Variable	Odds Ratio	95% Lower CI	95% Upper CI
Semaglutide	0.56000	0.45093	0.69545
Exenatide	0.67841	0.58792	0.78283
Liraglutide	0.73309	0.67876	0.79177
Dulaglutide	0.76827	0.69970	0.84356