Oral semaglutide adherence and associated risk factors in patients with type 2 diabetes in the United States

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Aim

- To evaluate adherence to and factors associated with lower adherence to oral semaglutide, with a focus on almost adherent patients with type 2 diabetes (T2D) in a real-world setting.

Introduction

- Among the 38 million adults living with diabetes in the United States (US), an estimated 90–95% have T2D.[1]
 - Glucagon-like peptide-1 (GLP-1) receptor agonists are a well-established treatment option for people with T2D, with oral semaglutide representing the first oral GLP-1 analog approved for treatment of T2D.[2–3]
- Adherence to anti-diabetic medications, including GLP-1 receptor agonists, is integral to their therapeutic effect, with increased adherence associated with a lower incidence of adverse clinical outcomes and increased glycemic control.[4–6] Understanding factors that impact patient adherence to oral semaglutide is essential in forming effective intervention programs in the clinical treatment of T2D.

Methods

- This US-based, retrospective cohort study utilized patient data from Optum's de-identified Clinformatics® Data Mart Database (study period January 2018–June 2023) of adults with T2D who initiated oral semaglutide (full selection criteria shown in **Figure 1**).
- The index date was defined as date of first fill of oral semaglutide on or after September 20, 2019, and patients had continuous follow-up data. The baseline period was defined as the 12-month period prior to the index date, and the follow-up period was defined as the 12-month period after the index date, divided into four quarters (Q).
- Proportion of days covered (PDC) was used to assess adherence (with a stockpiling adjustment) and was evaluated for each Q in the follow-up period.
- Patients were categorized into non-adherent (PDC <48%), almost adherent (48% ≤PDC <80%) and adherent (PDC ≥80%) groups.
 - A cut-off of 48% was chosen, since almost adherence becomes adherence on one additional prescription fill at each follow-up Q: 80% - [(30/91)*100]% = 48% (where 30 days are 1 month of fills, and 91 days = 1 Q).
 - Adherence categories were also assessed in a subgroup analysis of patients aged ≥65 years.
- Multinomial random-effects logistic regression was used to assess risk and protective factors during baseline and follow-up periods of adherence to oral semaglutide.

Results

- A total of 20,016 patients were included in this study; baseline demographic, clinical characteristics and healthcare resource utilization are presented in **Table 1**.
- The prescribing physician specialty was most commonly primary care provider (80.6%), followed by endocrinology (11.8%), other/unknown (7.5%) and cardiology/cardiovascular surgery (0.7%).
- The mean quarterly PDC for Q1–Q4 was 78%, 53%, 46% and 42%, respectively.
- The proportion of adherent and almost adherent patients dropped from Q1 to Q4 (59.8% vs 35.7% and 18.5% vs 7.8%, respectively), while the percentage of non-adherent patients increased (21.8% vs 56.5%; **Figure 2**).
- Factors associated with patients being almost adherent versus adherent are shown in **Figure 3**.
 - Patients of some ethnic minorities and who resided in the South or West were significantly more likely to be almost adherent versus adherent. This was also true for patients with a history of atherosclerotic cardiovascular disease (ASCVD), with HbA_{1c} ≥8% and with anxiety disorder, among other characteristics.

Figure 1: Patient selection

Criterion	n
≥2 diagnoses of T2D (on ≥2 distinct days)	n = 5,638,195
Did not have a diagnosis of T1D at any time	n = 5,128,704
Initiated oral semaglutide after the first observed T2D diagnosis	n = 66,484
Index date on or after September 20, 2019*	n = 66,484
Continuous claims enrollment from ≥12 months both prior to and after the index date	n = 20,036
No diagnosis of gestational diabetes during the baseline or follow-up periods	n = 20,018
Age ≥18 years old on index date	n = 20,016
Date of death is not before the end of the follow-up period†	n = 20,016
Final sample	n = 20,016

*Approval date of oral semaglutide by the US FDA. †Imputed as the 15th of the documented month of death
FDA, Food and Drug Administration; T1D, type 1 diabetes; T2D, type 2 diabetes

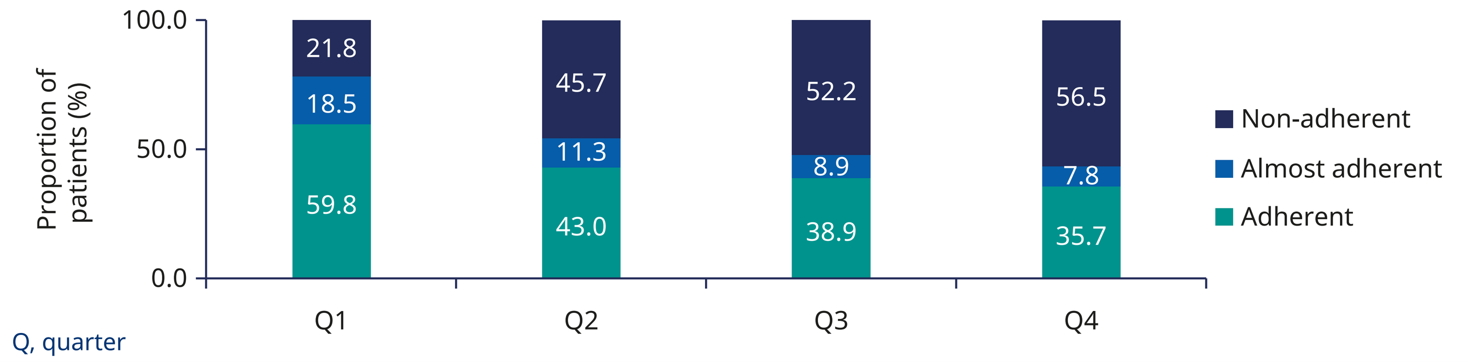
Table 1: Baseline demographics, clinical characteristics and HCRU

Characteristic	n (%)*
Male	9,725 (48.6)
Race	
White	11,676 (58.3)
Black	3,072 (15.3)
Hispanic	3,005 (15.0)
Asian	981 (4.9)
Other / unknown	1,282 (6.4)
Geographic region	
South	10,898 (54.4)
West	3,543 (17.7)
Midwest	3,889 (19.4)
Northeast	1,670 (8.3)
Other / unknown	16 (0.1)

Characteristic	n (%)*
Age on index (years)	
≥65	10,553 (52.7)
History of ASCVD	5,623 (28.1)
Obesity	11,149 (55.7)
Evidence of HbA_{1c} ≥8% at baseline or on index	6,301 (51.2)
Anxiety disorder	3,225 (16.1)
Insulin use on index date	2,390 (11.9)
Polypharmacy†	15,786 (78.9)
PDC for any T2D drugs ≥80% during baseline	10,470 (52.3)
GLP-1 RA-naïve before index date	17,152 (85.7)
Number of T2D-related inpatient visits (PPPY), mean (SD)	0.1 (0.4)
Number of non-T2D-related outpatient visits (PPPY), mean (SD)	11.0 (13.9)

*Data displayed as n (%), unless otherwise stated. †Concurrent use of ≥5 medications
ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 agonist; HbA_{1c}, glycated hemoglobin; HCRU, health-care resource utilization; PDC, proportion of days covered; PPPY, per person per year; SD, standard deviation; T2D, type 2 diabetes

Figure 2: Proportion of adherence, almost adherence and non-adherence of oral semaglutide from Q1 to Q4


100.0
50.0
0.0
Proportion of patients (%)
21.8
18.5
59.8
45.7
11.3
43.0
52.2
8.9
38.9
56.5
7.8
35.7
Q1
Q2
Q3
Q4
Non-adherent
Almost adherent
Adherent

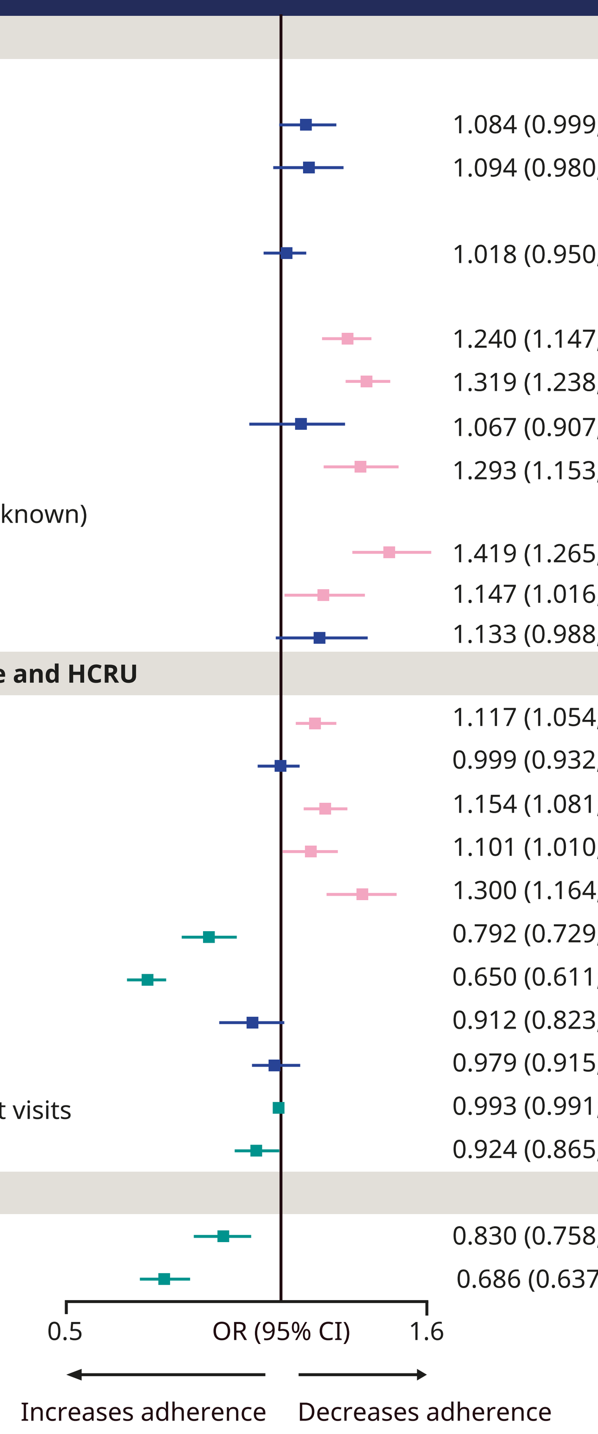
Q, quarter

- Factors such as polypharmacy, adherence to any T2D drugs, an increased number of non-T2D-related outpatient visits and out-of-pocket costs were significantly associated with a higher likelihood of being adherent.
- Risk factors associated with non-adherence versus adherence were similar to those comparing the almost adherent versus adherent groups, with the addition of older age (65–74 years: OR 1.212, 95% CI 1.085; 1.368, p<0.001; ≥75 years: OR 1.320, 95% CI 1.164; 1.486, p<0.001) acting as a risk factor and obesity acting as a protective factor (OR 0.934, 95% CI 1.875; 1.002, p=0.046).

Key result

Figure 3: Risk and protective factors associated with almost adherence versus adherence to oral semaglutide

Characteristic	OR (95% CI)	p-value for interaction
Baseline characteristics		
Age (reference: <65 years)		
65–74 years	1.084 (0.999; 1.190)	0.060
75+ years	1.094 (0.980; 1.218)	0.090
Sex (reference: male / unknown)		
Female	1.018 (0.950; 1.080)	0.548
Race (reference: White)		
Black	1.240 (1.147; 1.333)	<0.001
Hispanic	1.319 (1.238; 1.416)	<0.001
Asian	1.067 (0.907; 1.224)	0.426
Other/unknown	1.293 (1.153; 1.455)	<0.001
Region (reference: Northeast / other / unknown)		
South	1.419 (1.265; 1.617)	<0.001
West	1.147 (1.016, 1.305)	0.036
Midwest	1.133 (0.988; 1.317)	0.082
Clinical characteristics, medication use and HCRU		
History of ASCVD	1.117 (1.054; 1.190)	<0.001
Obesity	0.999 (0.932; 1.057)	0.978
Evidence of HbA_{1c} ≥8%	1.154 (1.081; 1.233)	<0.001
Anxiety disorder	1.101 (1.010; 1.196)	0.028
Insulin use on index date	1.300 (1.164; 1.446)	<0.001
Polypharmacy (excluding ADMs)*	0.792 (0.729; 0.863)	<0.001
PDC for any T2D drugs ≥80%	0.650 (0.611; 0.687)	<0.001
GLP-1 RA-naïve	0.912 (0.823; 1.006)	0.066
Number of T2D-related inpatient visits	0.979 (0.915; 1.059)	0.570
Number of non-T2D-related outpatient visits	0.993 (0.991; 0.996)	<0.001
Receipt of DESC service	0.924 (0.865; 0.990)	0.010
OOP costs, $ (reference: <50)		
50 to <100	0.830 (0.758; 0.904)	<0.001
≥100	0.686 (0.637; 0.742	<0.001


0.5
OR (95% CI)
1.6
Increases adherence
Decreases adherence

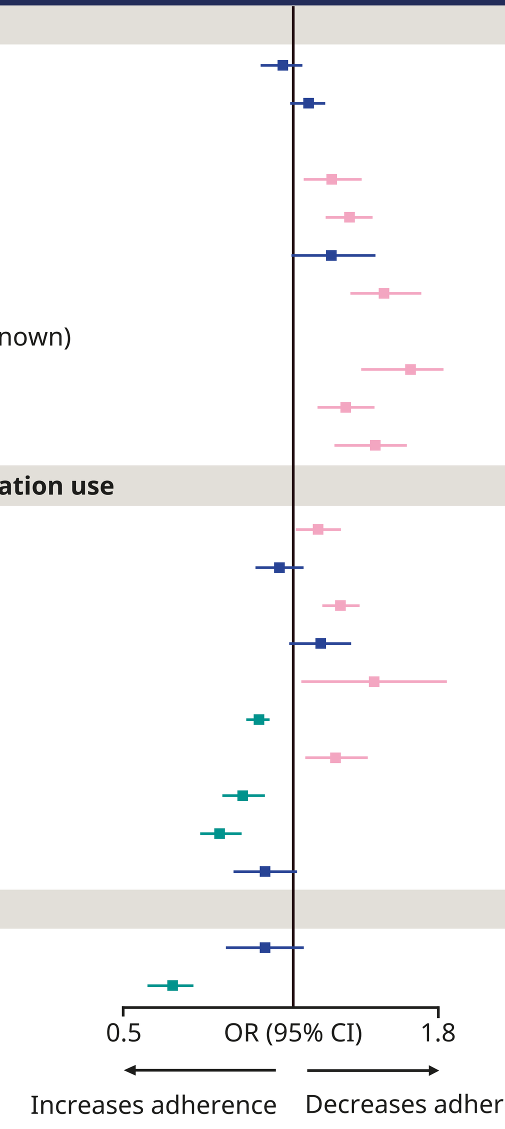
Risk factor
Protective factor
Non-significant

*Concurrent use of ≥5 medications
ADM, anti-diabetic medication; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; DESC, diabetes education and special care; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HCRU, healthcare resource utilization; OOP, out-of-pocket; OR, odds ratio; PDC, proportion of days covered; T2D, type 2 diabetes

- In a subgroup analysis of risk and protective factors associated with almost adherence versus adherence in participants ≥65 years (**Figure 4**), risk factors to adherence included history of ASCVD, HbA_{1c} ≥8%, presence of mood disorder and insulin use on index.

Figure 4: Risk and protective factors associated with almost adherence versus adherence to oral semaglutide in participants aged 65 years and over

Characteristic	OR (95% CI)	p-value for interaction
Baseline characteristics		
Age 75+ years (reference: 65–74)	0.959 (0.880; 1.032)	0.352
Female (reference: male / unknown)	1.064 (0.993; 1.133)	0.092
Race (reference: White)		
Black	1.169 (1.049; 1.314)	0.024
Hispanic	1.258 (1.147; 1.374)	<0.001
Asian	1.168 (0.998; 1.390)	0.050
Other/unknown	1.447 (1.269; 1.676)	<0.001
Region (reference: Northeast / other / unknown)		
South	1.613 (1.326; 1.834)	<0.001
West	1.239 (1.110; 1.385)	<0.001
Midwest	1.396 (1.189; 1.580)	<0.001
Clinical characteristics, including medication use		
History of ASCVD	1.106 (1.016; 1.208)	0.026
Obesity	0.946 (0.862; 1.037)	0.248
Evidence of HbA_{1c} ≥8%	1.212 (1.132; 1.303)	<0.001
Anxiety disorder	1.119 (0.989; 1.259)	0.096
Mood disorder	1.390 (1.039; 1.859)	0.042
Number of other ADM classes on index	0.869 (0.830; 0.903)	0.001
Insulin use on index	1.188 (1.056; 1.347)	<0.004
Polypharmacy (excluding ADMs)*	0.814 (0.753; 0.886)	<0.001
PDC for any T2D drugs ≥80%	0.741 (0.688; 0.806)	<0.001
GLP-1 RA-naive	0.892 (0.788; 1.010)	0.072
OOP costs, $ (reference: <50)		
50 to <100	0.892 (0.764; 1.038)	0.154
≥100	0.612 (0.555; 0.662)	<0.001


0.5
OR (95% CI)
1.8
Increases adherence
Decreases adherence

Risk factor
Protective factor
Non-significant

*Concurrent use of ≥5 medications
ADM, anti-diabetic medication; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; OOP, out-of-pocket; OR, odds ratio; PDC, proportion of days covered; T2D, type 2 diabetes

Limitations

- Due to the nature of database studies, the findings reported may include patients who were miscoded and/or misclassified and therefore may not be representative of the overall US population with T2D.

Conclusions

- In improving the identified risk factors associated with adherence to oral semaglutide, these findings may improve patient adherence and form future intervention programs in clinical practice.

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(**1**) US Centers for Disease Control and Prevention. Diabetes Basics. https://www.cdc.gov/diabetes/about/index.html (accessed Jan 9, 2025); (**2**) Isaacs et al. Diabetes Spectr 2021:34;7–19; (**3**) Novo Nordisk. Rybelsus®. https://www.rybelsus.com/prescribing-information (accessed Jan 9, 2025]; (**4**) Ciardullo et al. Diabetes Metab Res Rev 2024;40:e3791; (**5**) Palanca et al. Diabetes Ther 2023:14;723–36 (**6**) Giorgino et al. Patient Prefer Adherence 2018:12;707–19