

Use of Second-Generation Antidiabetic Medication Among a Nationally Representative Sample

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In the United States, type 2 diabetes (T2D) affects approximately 34.2 million individuals, or approximately 10% of the population,¹ with 1.5 million new cases diagnosed each year.² T2D accounts for 90% to 92% of total diabetes diagnoses.¹ The estimate of health care expenditure for diabetes was \$327 billion in 2017, marking a 26% increase from 2012 (\$245 billion), including \$237 billion in direct medical costs and \$90 billion in productivity loss.³ On an individual level, the mean medical cost for patients with diabetes is \$16,752, of which 57% is from diabetes care and 15% from antidiabetic medications.³

Diabetes can be managed, and its consequences can be avoided or delayed with diet, physical activity, medication, and regular screening and treatment for complications.⁴ The American Diabetes Association (ADA) in 2012 started to recommend a shared decision-making approach to individualize glycemic targets and medication selection based on clinical characteristics, socioeconomic status, and patient preference.⁵ According to the latest ADA guidelines, metformin is recommended for the initial pharmacologic treatment of patients with T2D.⁶ In the early 2000s, the treatment options for T2D, in addition to metformin, were limited to sulfonylureas, thiazolidinediones, and insulin. Although these antidiabetic agents have shown potent antihyperglycemic effects, their major disadvantages are elevated risks of hypoglycemia, weight gain, bone fracture, and heart failure.⁶

Since 2005, the FDA has approved glucagonlike peptide-1 (GLP-1) receptor agonists (2005),⁷ dipeptidyl peptidase 4 (DPP-4) inhibitors (2006),⁸ and sodium-glucose cotransporter 2 (SGLT2) inhibitors (2013).⁹ These second-generation antidiabetic medications have less hypoglycemic effect and weight gain but cost more than traditional agents.⁶ For example, the generic forms of first-generation antihyperglycemic medications are available for \$4 per month, whereas second-generation medications may cost more than \$500 per month.¹⁰⁻¹² DeJong et al found that annual costs for common novel agents ranged from \$5202 to \$11,225 compared with \$31 to \$136 for traditional drugs in Medicare Part D.¹³ Liss et al also found that the higher cost of nonsulfonylurea medications (ie, DPP-4 inhibitors, GLP-1 receptor agonists, and

ABSTRACT

OBJECTIVES: Existing studies have shown the benefits of second-generation antidiabetic medications in patients with type 2 diabetes (T2D). However, the medications' real-world utilization was not well understood. Our study assessed patient factors associated with the use of second-generation antidiabetic medications in a nationally representative sample of patients with T2D.

STUDY DESIGN: This retrospective, cross-sectional analysis used the 2005 to 2018 National Health and Nutrition Examination Survey (NHANES) data.

METHODS: Survey participants 18 years and older who had a diagnosis of T2D and had used antidiabetic medications in the past 30 days were included. The primary outcome was the prescription of any second-generation antidiabetic medication. Weighted stepwise multivariable logistic regression models were used to assess the associations between the use of second-generation antidiabetic medications and patients' characteristics.

RESULTS: Among 4493 patients with T2D, 533 (weighted %, 13.67%) reported using at least 1 second-generation antidiabetic drug. In multivariable analyses, patients with incomes at least 400% of the federal poverty level (adjusted odds ratio [AOR], 2.30; 95% CI, 1.58-3.34), with higher hemoglobin A_{1c} levels (AOR, 1.10; 95% CI, 1.02-1.18), and taking more medications (AOR, 1.14; 95% CI, 1.09-1.20) were more likely to use second-generation antidiabetic drugs compared with their counterparts.

CONCLUSIONS: The uptake of second-generation antidiabetic medications was 14% among patients with T2D in the United States. Prescription benefit design that targets lower out-of-pocket payments for these newer drugs may improve patient access and clinical outcomes for patients with T2D.

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TAKEAWAY POINTS

This study aims to assess the use of newer drugs for the treatment of patients with type 2 diabetes in the United States. We found that the use of newer drugs was 14%. In addition, newer drugs were prescribed more frequently to patients with higher income, worse glucose control, and more comorbidities. Our findings are expected to improve awareness of barriers to patient uptake of antihyperglycemic medications and access to these newer, expensive treatments in patients with type 2 diabetes.

- ▶ Nationally, approximately 14% of patients with type 2 diabetes receiving antidiabetic drugs have used at least 1 second-generation antidiabetic medication. Dipeptidyl peptidase 4 inhibitors were the most frequently prescribed newer agents.
- ▶ Income level, hemoglobin A_{1c}, and comorbidity burden were the independent patient-level drivers of the use of newer agents.

SGLT2 inhibitors) was the main driver of relative increases in total costs in a large cohort of commercially insured adults with T2D in the United States.¹⁴ In addition, studies have shown the benefits of second-generation antidiabetic medications beyond their antihyperglycemic effect, such as preventing atherosclerotic cardiovascular disease (ASCVD; SGLT2 inhibitors and GLP-1 receptor agonists), preventing heart failure (SGLT2 inhibitors), and improving renal function (SGLT2 inhibitors and GLP-1 receptor agonists).⁶ Given the proven benefits of these agents, their uptake was expected to increase since 2015. However, the main factor that has hindered the uptake of second-generation antidiabetic prescriptions and access to these new medications is cost.¹⁵ In addition, the decision to prescribe these new medications in clinical practice can be complicated by other factors such as patients' demographics, number of comorbidities, and the presence of specific comorbidities.⁶

Results of recent studies have updated the national utilization of antidiabetic medications. Gilstrap et al found that among Medicare beneficiaries from 2007 to 2015, 7% of patients with newly diagnosed T2D initiated second-generation antidiabetic agents.¹⁶ In this study, the uptakes of DPP-4 inhibitors and GLP-1 receptor agonists were associated with patients' comorbidities such as chronic kidney disease (CKD) and ischemic heart disease, respectively.¹⁶ In 2 other studies, the authors explored the use of all therapeutic classes for the treatment of T2D and whether the real-world prescribing reflected the recommendations of ADA in a national representative sample.^{17,18} Specifically, they explored adherence to the ADA guidelines such as metformin as first-line treatment and medication selection based on risk of hypoglycemia, weight status, cost, and CV benefits.¹⁷ However, treatment selection for patients with obesity or CVD was not consistent with ADA recommendations.¹⁷ In addition, the associations between patient factors (eg, demographics, socioeconomic status, health behavior, clinical characteristics of diabetes, comorbidities) and the use of second-generation antidiabetic agents remain unknown. Understanding these associations will help clinical practitioners and policy makers tailor treatment choices and develop initiatives to enhance the uptake of second-generation antidiabetic agents.

This study assessed patient factors associated with the use of second-generation antidiabetic medications in a nationally representative sample of patients with T2D. We hypothesized that patients with a high risk of hypoglycemia (ie, older adults and those with activities of daily living [ADL] dependency, who have more comorbidities, and who take more medications) are more likely to receive the second-generation antidiabetic agents.⁶ In addition, patients with the intention of weight loss (ie, those with obesity or on a diabetic diet), specific comorbidities (eg, CVD, CKD), and higher socioeconomic status may have a higher likelihood of using a second-generation antidiabetic agent.⁶

METHODS

Study Design, Data Sources, and Study Sample

We conducted a retrospective, cross-sectional analysis using the 2005 to 2018 National Health and Nutrition Examination Survey (NHANES) data. The NHANES is a nationally representative survey that uses a complex sampling design to collect deidentified information on individuals' demographics, health behaviors, nutrition intake, medication use, physical and laboratory examinations, diseases, and conditions among the noninstitutionalized US population through in-home interviews and mobile examination centers across the United States.¹⁹ Compared with payers' administrative claims data, the NHANES includes additional data on individuals' socioeconomic information, health behavior and lifestyle, laboratory tests, and health-related quality of life. This study was reviewed and exempted by the Auburn University Institutional Review Board.

The study sample included NHANES adult participants (aged ≥ 18 years) who either had a diagnosis of diabetes by ADA criteria or had been told they have diabetes.²⁰ Participants with diabetes were identified if any of the following criteria were met, using the NHANES laboratory tables: (1) hemoglobin A_{1c} (HbA_{1c}) of 6.5% or greater, (2) a 2-hour plasma glucose of at least 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test, (3) fasting plasma glucose of at least 126 mg/dL (7.0 mmol/L), or (4) had ever been told they have diabetes or reported taking any antidiabetic pills in the NHANES Diabetes Questionnaire. The study sample was further limited to patients with diabetes who had taken any antidiabetic medication in the past 30 days identified from the NHANES Prescription Drugs table, using Multum MediSource Lexicon's therapeutic category name (second-level category name = 99). We then removed patients with potential type 1 diabetes by excluding patients younger than 20 years and using only insulin, as well as pregnant women.²¹ In addition, participants with nonpositive sampling weight were excluded because they did not contribute to the weighted analysis. All laboratory results in the NHANES were obtained using certified and standardized procedures.²²

Measurements

Outcome. The primary outcome was the prescription of any second-generation antidiabetic medication. Patients were recorded as taking any second-generation antidiabetic medication if their prescription history in the past 30 days contained any component of GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors identified by Multum MediSource Lexicon's therapeutic category code, regardless of single-ingredient or combination products (**eAppendix Table** [available at ajmc.com]). Otherwise, patients were categorized into the subgroup of those who did not use second-generation antidiabetic medication.

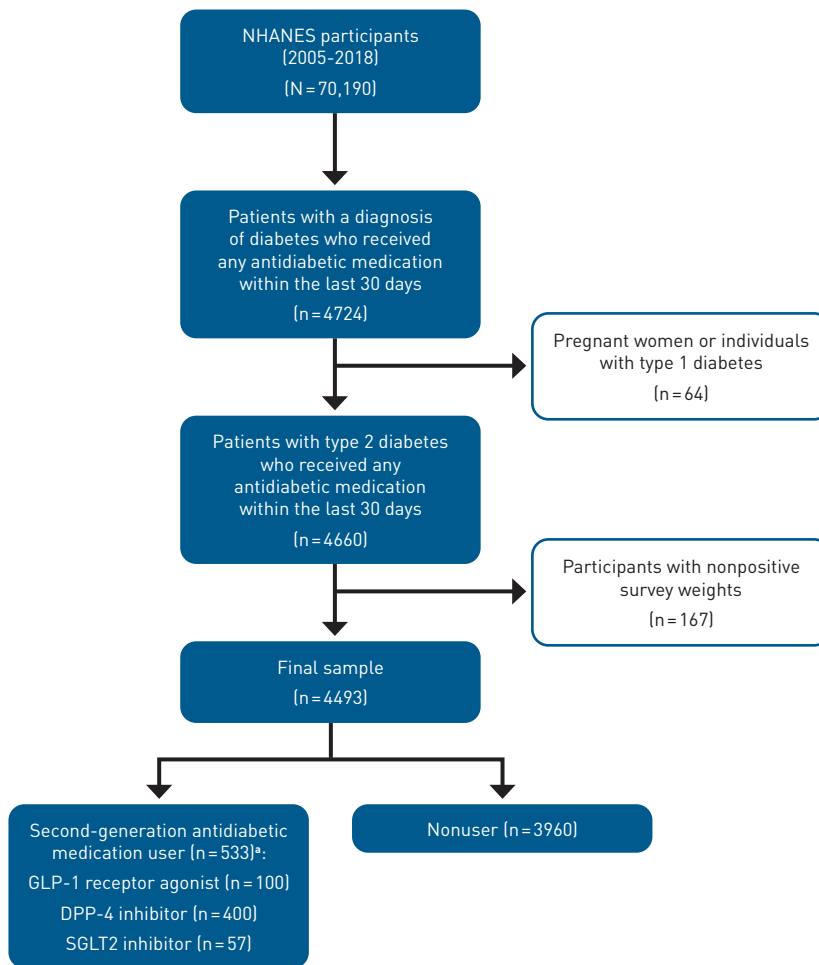
Patient factors. Patient factors assessed in this study included patients' demographics, socioeconomics, access to care, health behaviors, diabetes-related variables, and comorbidities that may be associated with the use of second-generation antidiabetic medications. Details in these 6 domains of patient factors are described as follows:

- Demographics (Demographic Variables & Sample Weights table in NHANES): age group (18-44, 45-64, or ≥ 65 years), sex (male or female), and race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, or other).
- Socioeconomic status (Demographic Variables & Sample Weights table): education status (less than high school, high school, or college and above), marital status (widowed/divorced/separated, married/living with a partner, or never married), and poverty level (defined by the ratio of income to federal poverty level [FPL]: $< 100\%$, $100\% - < 200\%$, $200\% - < 400\%$, or $\geq 400\%$).
- Access to care (Health Insurance table): health insurance status (uninsured vs any health insurance) and prescription coverage status (yes vs no).
- Health behaviors: Alcohol use was defined as nonuse, moderate use (≤ 2 drinks/day for men and ≤ 1 drink/day for women), or heavy use (> 2 drinks/day for men and > 1 drink/day for women) from the Alcohol table in NHANES, according to *Dietary Guidelines for Americans 2020-2025*.²³ Smoking status was categorized as never smoked, current smoker, or former smoker (Smoking—Cigarette Use table). Physical activity levels were defined as tertiles of total metabolic equivalent scores calculated by an algorithm provided for each cycle: low, moderate, or rigorous (Physical Activity table).²⁴ Body mass index was classified as less than 30 kg/m^2 (underweight, normal, overweight) or at least 30 kg/m^2 (obese) from the Body Measures table.²⁵ ADL dependency was defined by any difficulty in any of the 3 components of ADL in the physical functioning questionnaire: getting in and out of bed, eating, and dressing (Physical Functioning table).
- Diabetes-related factors: HbA_{1c} at the time of medical examination (continuous variable; Glycohemoglobin table), current diabetic diet (yes if the patient is on any diabetic diet; Dietary Interview—Total Nutrient Intakes table), and the presence of any diabetic complication (if the patient reported that their diabetes affected their eyes or they had retinopathy; Diabetes table).

- Comorbidities and medication use: We obtained 16 continuously reported comorbidities from the Medical Conditions table (2005-2018). Specific comorbidities that may be related to second-generation antidiabetic medication are any CVD (ie, angina, stroke, myocardial infarction, coronary heart disease), heart failure (HF), and CKD. CKD was defined by an estimated glomerular filtration rate (eGFR) of less than $60 \text{ mL/min/1.73 m}^2$ or albuminuria (Albumin & Creatinine—Urine table).²⁶ eGFR was calculated based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation and the Kidney Disease: Improving Global Outcomes definition with provided serum creatinine level and race of participants.^{26,27} Serum creatinine was calibrated across cycles.²⁸ Albuminuria was defined as an albumin-to-creatinine ratio of at least 30 mg/g .²⁶ Number of comorbidities and number of medications taken in the past 30 days were also obtained (Prescription Medications table).

Statistical Analysis

Descriptive statistics (continuous variables: mean and SD; categorical variables: frequency count and percentage) were used to describe the study sample. Bivariable analyses were conducted to compare the differences in distributions of assessed patient factors between patients who used and did not use any second-generation antidiabetic medications. We used domain-based multivariable logistic regression models to assess the associations between patient factors and the use of any second-generation antidiabetic medications. Specifically, we conducted stepwise logistic regression modeling by adding each domain of patient factors into the multivariable models and assessing the fluctuation of effect estimate (adjusted odds ratio [AOR] with 95% CI) with an additional domain. Health insurance status was not included in the model due to its high correlation with prescription coverage, and prescription coverage may be a better predictor for the use of second-generation medications in practice. Likewise, we selected number of medications taken and dropped number of comorbidities out of the model due to correlation. We also tested the interactions between race/ethnicity and prescription coverage using the *F* test. Sensitivity analyses were conducted by stratifying the prescriptions of second-generation antidiabetic medications into GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors as well as time before 2015 and after 2015 (when the evidence on beyond-antihyperglycemic effects of SGLT2 inhibitors and GLP-1 receptor agonists became available). All analyses were weighted using the 2-year cycle NHANES weights (interview weights and medical exam weights—Mobile Examination Center [MEC]).²⁹ Weights were adjusted for a combined 7 cycles (2005-2018).³⁰ According to the NHANES analytic guide, we used MEC because it yielded the least common denominator (the smallest subpopulation that includes all the variables).³⁰ Patient observations with missing data under some variables were removed from the multivariable analysis if the missing proportion was less than 1% in those variables and were classified as unknown to replace missing values if otherwise. Statistical analyses were conducted using SAS 9.4 (SAS Institute) with the significance level being 0.05.

FIGURE. Flowchart Diagram of Study Sample

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagonlike peptide; NHANES, National Health and Nutrition Examination Survey; SGLT2, sodium-glucose cotransporter 2.

*Each patient could have used more than 1 drug class, so the sum of individuals in the 3 subgroups exceeded 533.

RESULTS

Study Sample and Patients' Characteristics

The study sample included 4493 patients with T2D treated with antidiabetic medications, which represented 19,629,829 patients across the United States from 2005 to 2018 (Figure 1). Among them, 533 (weighted proportion, 13.67%) reported the use of at least 1 second-generation antidiabetic drug in the past 30 days. Specifically, 100 patients (weighted, 21.6%; 95% CI, 16.67%-26.71%) used GLP-1 receptor agonists, 400 patients (weighted, 70.62%; 95% CI, 64.70%-76.54%) used DPP-4 inhibitors, and 57 patients (weighted, 12.34%; 95% CI, 7.53%-17.16%) used SGLT2 inhibitors.

Characteristics of patients with and without the use of second-generation antidiabetic medications are described in Table 1.

Since the drugs' launch into the US market in 2005, the proportion of users has increased consistently across years.

Patient Factors Associated With the Use of Second-Generation Antidiabetic Medications (unadjusted)

For age, race/ethnicity, poverty level, health insurance, and prescription coverage status, the corresponding largest groups of patients in the study sample who reported taking second-generation antidiabetic medications were those who were aged 45 to 64 years, were non-Hispanic White, had incomes above 400% of the FPL, were insured, and had prescription coverage (all $P < .05$) (Table 1). In addition, patients who used second-generation antidiabetic medications had higher mean HbA_{1c} levels and had taken more medications compared with nonusers (all $P < .05$).

Patient Factors Associated With the Use of Second-Generation Antidiabetic Medications (adjusted)

In the weighted stepwise logistics multivariable models ($n = 4446$) (Table 2), patients with T2D with the following factors were consistently and significantly associated with receiving second-generation antidiabetic medications in the full model: income of 200% to 400% of the FPL (AOR, 1.69; 95% CI, 1.10-2.59), income of 400% or more of the FPL (AOR, 2.30; 95% CI, 1.58-3.34), higher HbA_{1c} level (a 1% increase in HbA_{1c} was associated with a 10.1% increase in odds of receiving newer-generation medications compared with not receiving them; AOR, 1.10; 95% CI, 1.03-1.18), and number of medications taken (AOR, 1.14; 95% CI, 1.09-1.20). Prescription

coverage was a significant predictor when health behavior factors were added to the model (AOR, 1.49; 95% CI, 1.06-2.09) but was not significant in the full model (AOR, 1.30; 95% CI, 0.89-1.90). In contrast, patients with current smoking status were less likely to use second-generation antidiabetic agents in the full model (AOR, 0.51; 95% CI, 0.28-0.94), but the association was not significant in the initial model (AOR, 0.61; 95% CI, 0.35-1.04). The interaction between race/ethnicity and prescription coverage was not significant ($P = .47$).

Sensitivity Analyses

In the first sensitivity analysis, we assessed the associations between patient factors and the use of individual second-generation antidiabetic agents. Patients' income level being 400% or more

of the FPL and their number of medications were consistently and significantly associated with the use of GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors. However, higher HbA_{1c} level was associated with the use of GLP-1 receptor agonists but not DPP-4 inhibitors or SGLT2 inhibitors (Table 3). In the second sensitivity analysis, we restricted the study sample to NHANES cycles from 2015 to 2018 when the beyond-hyperglycemic benefits of second-generation antidiabetic agents were published. The findings were consistent with the main analysis, and patients aged 45 to 64 years were more likely to use second-generation antidiabetic agents compared with those aged 18 to 44 years (Table 3).

DISCUSSION

From 2005 to 2018, approximately 14% of patients with T2D treated with antidiabetic medications across the United States received at least 1 second-generation antidiabetic drug. The most commonly prescribed second-generation antidiabetic drug class was DPP-4 inhibitors. Higher income level, inadequate glycemic control (ie, higher HbA_{1c} level), and a greater number of medications were the main patient factors associated with the use of second-generation antidiabetic agents.

In a recent study, Gilstrap et al found that between 2007 and 2015 only 7% of Medicare beneficiaries received second-generation antidiabetic agents among treated patients with T2D.¹⁶ The main difference in the uptake of these medications between the current study results and those of Gilstrap et al may be attributable to patients with different age groups. Our study included nationally representative adults 18 years and older, with patients 65 years and older accounting for only 36.26% of patients among those who used second-generation antidiabetic agents. However, due to similar study duration period, DPP-4 inhibitors were the most prescribed second-generation antidiabetic agents in both studies. Although a GLP-1 receptor agonist (exenatide) was approved and available on the US market before a DPP-4 inhibitor, the utilization rate of DPP-4 inhibitors was higher. This could be explained by the availability of oral dosage forms of DPP-4 inhibitors and the

TABLE 1. Study Sample Characteristics Among Patients With Type 2 Diabetes Who Used or Did Not Use Second-Generation Antidiabetic Medications (N = 4493)

Characteristic	Second-generation antidiabetic medication users (n = 533)		Nonusers (n = 3960)		P ^a
	n	Weighted % (95% CI)	n	Weighted % (95% CI)	
NHANES cycle					
2005-2006	4	0.96 [0.00-2.09]	398	11.11 [9.32-12.89]	<.0001
2007-2008	37	7.11 [3.73-10.49]	613	12.90 [10.60-15.19]	
2009-2010	63	11.02 [7.04-15.00]	593	12.70 [11.15-14.26]	
2011-2012	71	13.74 [9.86-17.62]	547	13.66 [11.42-15.90]	
2013-2014	100	18.22 [14.07-22.37]	551	15.39 [13.31-17.46]	
2015-2016	129	21.41 [16.52-26.30]	601	16.93 [14.74-19.12]	
2017-2018	129	27.54 [21.42-33.67]	657	17.32 [15.51-19.38]	
Age group in years					
18-44	43	9.46 [5.59-13.33]	385	13.11 [11.30-14.92]	.01
45-64	241	54.27 [48.11-60.43]	1686	44.20 [41.80-46.59]	
≥ 65	249	36.26 [30.33-42.20]	1867	42.68 [40.29-45.08]	
Missing (n = 22)					
Sex					
Male	276	55.30 [49.04-61.57]	1980	49.90 [47.57-52.24]	.11
Female	257	44.70 [38.43-50.97]	1980	50.10 [47.76-52.43]	
Race/ethnicity					
Hispanic	139	11.55 [8.18-14.93]	1079	14.23 [11.98-16.48]	.04
Non-Hispanic Black	140	12.27 [9.06-15.48]	1096	15.91 [13.80-18.01]	
Non-Hispanic White	182	66.97 [61.00-72.95]	1358	60.94 [57.81-64.07]	
Others	72	9.20 [6.20-12.20]	427	8.92 [7.46-10.38]	
Education					
Less than high school	152	17.77 [13.35-22.19]	1388	24.05 [21.91-26.20]	.06
High school	135	29.87 [22.43-37.30]	877	24.18 [22.05-26.31]	
College or higher	244	52.36 [44.95-59.77]	1654	51.77 [49.00-54.53]	
Missing (n = 43)					
Marital status					
Widowed/divorced/separated	322	69.40 [63.91-74.89]	2316	62.34 [60.45-64.22]	.10
Never married	42	7.09 [3.49-10.68]	347	9.10 [7.86-10.33]	
Married/living with a partner	169	23.51 [18.91-28.11]	1263	28.57 [26.56-30.58]	
Missing (n = 36)					
Poverty status (income as % of federal poverty level)					
< 100%	165	18.78 [13.76-23.79]	1234	23.45 [21.39-25.52]	.0002
100%-<200%	105	14.72 [11.40-18.03]	1126	24.14 [22.21-26.07]	
200%-<400%	127	29.52 [21.09-37.95]	953	27.33 [25.15-29.51]	
≥ 400%	136	36.98 [29.43-44.54]	647	25.08 [22.76-27.39]	
Health insurance					
Insured	508	96.39 [94.30-98.48]	3522	91.16 [89.98-92.33]	.001
Uninsured	25	3.61 [1.52-5.70]	438	8.84 [7.67-10.02]	
Prescription coverage					
Yes	473	91.25 [88.52-93.98]	3253	85.21 [83.68-86.74]	.0008
No	60	8.75 [6.02-11.48]	707	14.79 [13.26-16.32]	

(continued)

TABLE 1. (Continued) Study Sample Characteristics Among Patients With Type 2 Diabetes Who Used or Did Not Use Second-Generation Antidiabetic Medications (N = 4493)

Characteristic	Second-generation antidiabetic medication users (n = 533)		Nonusers (n = 3960)		P ^a
	n	Weighted % (95% CI)	n	Weighted % (95% CI)	
Physical activity					
Low	232	38.38 (31.51-45.25)	1757	40.55 (38.29-42.81)	.51
Moderate	166	33.85 (27.58-40.11)	1323	35.23 (33.02-37.44)	
Rigorous	135	27.77 (22.44-33.11)	876	24.22 (22.00-26.45)	
Missing (n = 4)					
Alcohol use					
Nonuse	269	41.67 (34.97-48.36)	2185	48.27 (45.60-50.95)	.18
Moderate	126	27.85 (21.40-34.31)	814	25.67 (23.06-28.28)	
Heavy	138	30.48 (24.59-36.36)	965	26.06 (24.18-27.93)	
Body mass index					
< 30 kg/m ²	205	30.54 (25.31-35.77)	1719	38.68 (36.45-40.92)	.0036
≥ 30 kg/m ²	328	69.46 (64.23-74.69)	2241	61.31 (59.08-63.55)	
Smoking					
Never	291	52.64 (45.09-60.18)	2015	50.53 (48.61-52.44)	.16
Former	187	37.82 (31.01-44.62)	1367	35.19 (33.42-36.97)	
Current	55	9.55 (6.01-13.08)	578	14.28 (12.72-15.83)	
ADL dependent					
Yes	155	23.93 (19.53-28.34)	1124	24.23 (22.22-26.24)	.90
No	378	76.07 (71.66-80.47)	2836	75.77 (73.76-77.78)	
Presence of diabetic complications					
On diabetic diet	112	17.68 (12.84-22.52)	814	19.05 (17.29-20.81)	.61
Hemoglobin A _{1c} , mean (SD)	110	25.08 (18.78-31.37)	739	19.71 (17.82-21.59)	.10
Comorbidities					
CVD	165	28.35 (23.11-33.59)	1117	26.78 (24.91-28.66)	.56
HF	66	12.14 (7.98-16.31)	414	9.55 (8.38-10.71)	.19
CKD	212	34.66 (29.24-40.09)	1451	34.68 (32.55-36.83)	.99
Number of comorbidities, mean (SD)		3.93 (0.16)		3.74 (0.05)	.26
Number of medications, mean (SD)		7.24 (0.23)		5.92 (0.07)	<.0001

ADL, activities of daily living; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; NHANES, National Health and Nutrition Examination Survey.

^aP for weighted Rao-Scott χ^2 test and weighted *t* test for continuous/count variables. *P* values in bold are < .05.

hesitancy of using GLP-1 receptor agonists as injectable drugs.¹⁶ Because the first SGLT2 inhibitor (canagliflozin) was approved in 2013, the small proportion of SGLT2 inhibitor users found in this study was expected. Le et al also found a small uptake of SGLT2 inhibitors in NHANES cycles from 2013 to 2016.¹⁷

Additionally, income level was associated with the use of second-generation antidiabetic agents among patients with T2D receiving antidiabetic medication treatments. Indeed, second-generation antidiabetic drugs are costly and dominated by brand-name products on the market, whereas traditional/first-generation agents

(ie, metformin, sulfonylureas) are available as generic formulations and mostly covered by health insurance. Given the significant difference in co-pay between brand and generic antidiabetic drugs, patients with higher incomes are more likely to be able to afford expensive, brand-name, newer antidiabetic drugs than those with lower incomes. Our findings supported that patients' income and affordability were important factors in access to second-generation antidiabetic drugs when out-of-pocket cost is a barrier.

In addition, patients with higher HbA_{1c} levels, which indicate inadequate glycemic control, had greater odds of receiving second-generation antidiabetic drugs. This finding is consistent with the ADA recommendation of combination therapy for patients whose glucose levels are not controlled by first-line treatment such as metformin. Specifically, ADA recommends combination therapy for patients with HbA_{1c} levels of 1.5% to 2.0% above target.⁶ The selection of second-generation antidiabetic agents also depends on clinical characteristics (such as high ASCVD risk, HF, CKD, other comorbidities, and risk for specific adverse effects) and patients' preference. However, we could not find significant associations between individual comorbidities such as CVD, HF, and CKD with the use of second-generation antidiabetic medications, overall or for individual drug classes. Our findings might be biased toward the null due to the small number of patients who had these comorbidities in our sample or indicate consistency with previous research showing that antidiabetic treatment selection for patients was not consistent with ADA recommendations.¹⁷ Future research is needed to understand how practitioners' prescribing behaviors and patients' preference affect the utilization of second-generation antidiabetic medications.

Furthermore, we found that a greater number of medications taken by patients was associated with higher likelihood of use of second-generation antidiabetic agents. Number of medications can be a proxy of disease burden and illness severity.³¹⁻³³ Therefore, our findings imply that patients with a higher number of or more severe conditions (ie, diabetes- or non-diabetes-related conditions) were more likely to receive second-generation antidiabetic agents. In fact, patients with higher disease burden of comorbidities were at higher risk of hypoglycemia.³⁴⁻³⁶ Because second-generation antidiabetic agents have minimal hypoglycemic effects,⁶ these

TABLE 2. Adjusted Associations Between Patient Factors and Use of Second-Generation Antidiabetic Medications (n=4446)^a

Variables	Adjusted ORs with 95% CIs					
	Demographics	Socioeconomics	Access to care	Health behaviors	Comorbidities	Diabetes variables
Demographics						
Age in years						
45-64 vs 18-44	1.64 (0.96-2.75)	1.55 (0.91-2.64)	1.53 (0.90-2.62)	1.57 (0.93-2.66)	1.35 (0.78-2.34)	1.41 (0.80-2.50)
≥65 vs 18-44	1.09 (0.63-1.88)	1.13 (0.66-1.92)	1.10 (0.65-1.88)	1.16 (0.65-2.07)	0.92 (0.50-1.71)	0.97 (0.50-1.88)
Sex, male vs female	0.86 (0.66-1.13)	0.92 (0.69-1.23)	0.91 (0.68-1.21)	0.91 (0.67-1.24)	0.87 (0.63-1.20)	0.90 (0.64-1.25)
Race/ethnicity						
Non-Hispanic Black vs White	0.69 (0.52-0.91)	0.79 (0.60-1.04)	0.80 (0.61-1.05)	0.81 (0.61-1.07)	0.84 (0.63-1.13)	0.76 (0.55-1.05)
Hispanic vs White	0.73 (0.54-1.00)	0.88 (0.64-1.20)	0.92 (0.68-1.25)	0.91 (0.66-1.24)	1.00 (0.72-1.39)	0.91 (0.65-1.27)
Others vs White	0.92 (0.61-1.38)	1.00 (0.65-1.53)	1.00 (0.65-1.53)	1.12 (0.70-1.77)	1.25 (0.77-2.02)	1.27 (0.78-2.07)
Socioeconomic factors						
Education						
No high school vs college		0.99 (0.68-1.44)	1.01 (0.69-1.46)	1.06 (0.71-1.58)	1.10 (0.74-1.64)	1.12 (0.74-1.69)
High school vs college		1.40 (0.96-2.05)	1.40 (0.95-2.05)	1.42 (0.96-2.11)	1.44 (0.96-2.16)	1.46 (0.96-2.21)
Marital status						
Widowed/divorced/separated vs married/living with a partner		0.88 (0.64-1.22)	0.88 (0.64-1.22)	0.90 (0.66-1.24)	0.92 (0.66-1.28)	0.89 (0.64-1.26)
Never married vs married/living with a partner		0.79 (0.44-1.43)	0.78 (0.44-1.41)	0.81 (0.45-1.45)	0.80 (0.43-1.51)	0.81 (0.42-1.59)
Poverty status (income as % of federal poverty level)						
<100% vs 100%-<200%		1.33 (0.96-1.85)	1.31 (0.95-1.82)	1.36 (0.99-1.87)	1.31 (0.96-1.80)	1.28 (0.92-1.76)
200%-<400% vs 100%-<200%		1.70 (1.10-2.62)	1.65 (1.07-2.55)	1.61 (1.04-2.49)	1.75 (1.15-2.66)	1.69 (1.10-2.59)
≥400% vs 100%-<200%		2.22 (1.55-3.19)	2.09 (1.45-3.00)	2.05 (1.41-2.99)	2.27 (1.59-3.26)	2.30 (1.58-3.34)
Access to care						
Prescription coverage, yes vs no			1.52 (1.08-2.14)	1.49 (1.06-2.09)	1.28 (0.90-1.83)	1.30 (0.89-1.90)
Health behaviors						
Physical activity						
Moderate vs low				0.88 (0.61-1.26)	0.93 (0.68-1.45)	0.94 (0.64-1.40)
Rigorous vs low				1.09 (0.74-1.61)	1.31 (0.86-1.98)	1.26 (0.82-1.94)
Alcohol use						
Moderate vs nonuse				1.05 (0.71-1.56)	1.11 (0.74-1.65)	1.05 (0.70-1.57)
Heavy vs nonuse				1.20 (0.84-1.71)	1.29 (0.88-1.89)	1.24 (0.83-1.83)
Smoking						
Current smoker vs nonsmoker				0.61 (0.35-1.04)	0.50 (0.28-0.90)	0.51 (0.28-0.94)
Former smoker vs nonsmoker				0.99 (0.71-1.38)	0.89 (0.63-1.24)	0.90 (0.64-1.27)
Body mass index						
≥30 kg/m ² vs <30 kg/m ²				1.34 (1.04-1.73)	1.16 (0.89-1.50)	1.17 (0.90-1.52)
Comorbidities						
CVD, yes vs no					0.79 (0.53-1.19)	0.79 (0.53-1.16)
HF, yes vs no					0.86 (0.61-1.23)	1.19 (0.66-2.15)
CKD, yes vs no					0.94 (0.69-1.26)	0.96 (0.70-1.31)
Number of medications taken					1.14 (1.09-1.19)	1.14 (1.09-1.20)
Diabetes-related variables						
With complications, yes vs no						0.77 (0.52-1.15)
Diabetic diet, yes vs no						1.29 (0.86-1.93)
Hemoglobin A _{1c}						1.10 (1.03-1.18)

CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure.

^aSignificant associations are in bold.

TABLE 3. Sensitivity Analyses of Adjusted Associations Between Patient Factors and Use of Second-Generation Antidiabetic Medications

Variables	Adjusted ORs with 95% CIs			
	GLP-1 receptor agonists	DPP-4 inhibitors	SGLT2 inhibitors	2015-2018
Demographics				
Age in years				
45-64 vs 18-44	0.73 (0.32-1.68)	1.55 (0.78-3.11)	3.46 (0.84-14.31)	2.60 (1.25-5.38)
≥ 65 vs 18-44	0.24 (0.08-0.72)	1.38 (0.62-3.00)	0.77 (0.14-3.62)	1.18 (0.47-2.98)
Sex, male vs female	1.26 (0.59-2.69)	0.81 (0.56-1.19)	0.69 (0.29-1.69)	0.71 (0.44-1.15)
Race/ethnicity				
Non-Hispanic Black vs White	0.63 (0.32-1.27)	0.72 (0.51-1.02)	1.03 (0.41-2.60)	0.75 (0.50-1.12)
Hispanic vs White	0.92 (0.56-1.51)	0.94 (0.63-1.39)	1.19 (0.40-3.52)	0.79 (0.47-1.33)
Others vs White	0.41 (0.15-1.34)	1.49 (0.84-2.62)	0.99 (0.28-3.53)	0.81 (0.38-1.76)
Socioeconomic factors				
Education				
No high school vs college	0.58 (0.28-1.15)	1.33 (0.82-2.52)	0.83 (0.31-2.21)	1.54 (0.94-2.52)
High school vs college	0.77 (0.36-1.66)	1.58 (0.99-2.52)	1.45 (0.51-4.11)	1.36 (0.73-2.54)
Marital status				
Widowed/divorced/separated vs married/living with a partner	1.04 (0.42-2.56)	0.93 (0.63-1.39)	0.66 (0.27-1.61)	1.07 (0.66-1.72)
Never married vs married/living with a partner	0.83 (0.27-2.59)	0.84 (0.37-1.94)	0.66 (0.23-1.90)	0.57 (0.23-1.39)
Poverty status (income as % of federal poverty level)				
< 100% vs 100%-<200%	0.88 (0.41-1.92)	1.45 (0.97-2.15)	0.83 (0.29-2.43)	1.11 (0.65-1.89)
200%-<400% vs 100%-<200%	1.56 (0.66-3.71)	1.64 (1.01-2.67)	1.97 (0.50-7.77)	1.69 (0.91-3.13)
≥ 400% vs 100%-<200%	3.44 (1.55-7.59)	2.05 (1.33-3.16)	2.40 (0.87-6.62)	1.98 (1.07-3.69)
Access to care				
Prescription coverage, yes vs no	0.89 (0.39-2.02)	1.47 (0.98-2.20)	1.81 (0.20-16.25)	1.21 (0.64-2.32)
Health behaviors				
Physical activity				
Moderate vs low	1.98 (0.99-3.93)	0.75 (0.47-1.18)	1.03 (0.24-4.39)	0.93 (0.50-1.71)
Rigorous vs low	1.70 (0.75-3.85)	1.24 (0.77-1.99)	1.74 (0.48-6.39)	0.95 (0.47-1.91)
Alcohol use				
Moderate vs nonuse	0.80 (0.33-1.93)	1.08 (0.69-1.68)	1.10 (0.37-3.30)	0.89 (0.45-1.75)
Heavy vs nonuse	1.19 (0.53-2.69)	1.27 (0.81-1.97)	1.65 (0.67-4.10)	1.12 (0.63-1.98)
Smoking				
Current smoker vs nonsmoker	0.73 (0.24-2.23)	0.53 (0.28-1.02)	0.42 (0.11-1.62)	0.59 (0.28-1.26)
Former smoker vs nonsmoker	1.00 (0.52-1.90)	0.95 (0.64-1.43)	0.71 (0.28-1.78)	0.66 (0.40-1.08)
Body mass index				
≥ 30 kg/m ² vs < 30 kg/m ²	1.21 (0.62-2.38)	1.12 (0.86-1.46)	1.42 (0.59-3.42)	1.17 (0.83-1.66)
Comorbidities				
CVD, yes vs no	0.95 (0.44-2.02)	0.74 (0.48-1.15)	1.58 (0.56-4.40)	0.70 (0.39-1.24)
HF, yes vs no	0.58 (0.21-1.62)	1.44 (0.73-2.85)	1.25 (0.21-7.55)	1.55 (0.60-4.15)
CKD, yes vs no	0.83 (0.44-1.56)	0.95 (0.63-1.36)	1.06 (0.53-2.14)	0.80 (0.53-1.20)
Number of medications taken	1.27 (1.15-1.39)	1.12 (1.07-1.17)	1.07 (0.93-1.22)	1.17 (1.08-1.26)
Diabetes-related variables				
With complications, yes vs no	0.65 (0.30-1.41)	0.75 (0.48-1.18)	1.11 (0.20-6.05)	1.08 (0.62-1.89)
Diabetic diet, yes vs no	1.40 (0.64-3.03)	1.35 (0.87-2.10)	1.07 (0.35-3.25)	1.34 (0.67-2.66)
Hemoglobin A _{1c}	1.15 (1.03-1.28)	1.09 (0.99-1.20)	0.93 (0.78-1.11)	1.17 (1.05-1.31)

CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagonlike peptide; HF, heart failure; SGLT2, sodium-glucose cotransporter 2.

medications could be prescribed to patients with a higher risk of hypoglycemia, such as those with higher burden of comorbidities. Although the association between the use of second-generation antidiabetic medications and weight status was not significant in our study, overall and by individual drug class, this might be due to the domination of DPP-4 inhibitor use in our sample; this class is known for its weight-neutral effect.³⁷ ADA recommends second-generation antidiabetic treatments for patients with compelling need to minimize weight gain or induce weight loss.⁶ Weight loss is the first beyond-antihyperglycemic effect of GLP-1 receptor agonists, and the FDA approved liraglutide in 2014 for the treatment of obesity.^{38,39} In 2021, semaglutide, another GLP-1 receptor agonist, was approved for obesity treatment.⁴⁰ In addition, the weight-loss effect of SGLT2 inhibitors was found in results from some of the very first randomized clinical trials on this drug class.⁴¹ Although the existing evidence supports the use of GLP-1 receptor agonists and SGLT2 inhibitors for patients with obesity, our study lacks statistical power to detect the association. Future studies may use the NHANES data to assess the association between weight status/weight loss–related activities and the use of such medications when newer data become available.

Limitations

Our study has several limitations. First, cross-sectional and observational study design could assess only association rather than causality. Second, unobserved confounding was inevitable (ie, patient and physician preference, conditions related to secondary hyperglycemia), although the richness of the NHANES data provided access to patient factors including laboratory data and health behaviors, which are often missing in administrative claims data. We implemented a stepwise modeling approach, tested for interaction, and conducted sensitivity analyses to confirm the robustness of main findings. Third, due to the small sample sizes of individual second-generation antidiabetic medication subgroups, we may not have enough statistical power to detect associations between medication use and different patient factors. Therefore, future research in assessing the associations with use of individual second-generation antidiabetic medications is critical. Fourth, selection bias may have occurred because we could not ensure that our exclusion criteria removed all patients diagnosed with type 1 diabetes. Finally, recall bias may persist because some of the patient factors were collected from self-reported data.

However, to our knowledge, this is the first study to evaluate the associations between patient factors and second-generation antidiabetic medications among a nationally representative US sample. The NHANES data capture additional, rich patient-level variables such as socioeconomic information, health behaviors including diet and lifestyle, laboratory tests, and health-related quality of life compared with administrative claims data. Our findings will assist practitioners and policy makers to tailor antidiabetic treatment and design prescription benefit coverage to improve access to these newer, expensive treatments.

CONCLUSIONS

The uptake of second-generation antidiabetic medications was 14% among patients with T2D in the United States. Patients' income, HbA_{1c} level, and number of medications taken were significantly associated with the use of second-generation antidiabetic medications. Future research to explore practitioners' prescribing behaviors and patients' preferences around second-generation antidiabetic medication prescription is warranted. ■

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eAppendix Table. Identification of Second-Generation Antidiabetic Medications in NHANES

Drug class	Drug code (RXDDRGID)	Standardized generic prescription medication names (RXDDRUG)
GLP-1 receptor agonists	d08251	ALBIGLUTIDE
	d08290	DULAGLUTIDE
	d08311	INSULIN DEGLUDEC; LIRAGLUTIDE
	d07466	LIRAGLUTIDE
	d08688	SEMAGLUTIDE
	d05529	EXENATIDE
	d08501	INSULIN GLARGINE; LIXISENATIDE
DPP-4 inhibitors	d07963	ALOGLIPTIN
	d07965	ALOGLIPTIN; PIOGLITAZONE
	d08344	EMPAGLIFLOZIN; LINAGLIPTIN
	d08692	ERTUGLIFLOZIN; SITAGLIPTIN
	d07767	LINAGLIPTIN
	d07825	LINAGLIPTIN; METFORMIN
	d07709	METFORMIN; SAXAGLIPTIN
	d06720	METFORMIN; SITAGLIPTIN
	d07467	SAXAGLIPTIN
	d07805	SIMVASTATIN; SITAGLIPTIN
	d05896	SITAGLIPTIN
SGLT-2 inhibitors	d08080	CANAGLIFLOZIN
	d08280	CANAGLIFLOZIN; METFORMIN
	d07928	DAPAGLIFLOZIN
	d08245	DAPAGLIFLOZIN; METFORMIN
	d08275	EMPAGLIFLOZIN
	d08344	EMPAGLIFLOZIN; LINAGLIPTIN
	d08384	EMPAGLIFLOZIN; METFORMIN
	d08689	ERTUGLIFLOZIN
	d08692	ERTUGLIFLOZIN; SITAGLIPTIN

GLP-1, glucagonlike peptide; DPP-4, dipeptidyl peptidase 4; NHANES, National Health and Nutrition Examination Survey; SGLT-2, sodium-glucose cotransporter 2.