Use of Antihyperglycemic Medications in U.S. Adults: An Analysis of the National Health and Nutrition Examination Survey

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Diabetes Care 2020;43:1227–1233 | https://doi.org/10.2337/dc19-2424

OBJECTIVE

1) To examine trends in the use of diabetes medications and 2) to determine whether physicians individualize diabetes treatment as recommended by the American Diabetes Association (ADA).

RESEARCH DESIGN AND METHODS

We conducted a retrospective, cross-sectional analysis of 2003–2016 National Health and Nutrition Examination Survey (NHANES) data. We included people ≥18 years who had ever been told they had diabetes, had an HbA_{1c} >6.4%, or had a fasting plasma glucose >125 mg/dL. Pregnant women and patients aged <20 years receiving only insulin were excluded. We assessed trends in use of ADA's seven preferred classes from 2003–2004 to 2015–2016. We also examined use by hypoglycemia risk (sulfonylureas, insulin, and meglitinides), weight effect (sulfonylureas, thiazolidinediones [TZDs], insulin, and meglitinides), cardiovascular benefit (canagliflozin, empagliflozin, and liraglutide), and cost (brand-name medications and insulin analogs).

RESULTS

The final sample included 6,323 patients. The proportion taking any medication increased from 58% in 2003–2004 to 67% in 2015–2016 ($P < 0.001$). Use of metformin and insulin analogs increased, while use of sulfonylureas, TZDs, and human insulin decreased. Following the 2012 ADA recommendation, the choice of drug did not vary significantly by older age, weight, or presence of cardiovascular disease. Patients with low HbA_{1c}, or HbA_{1c} <6%, and age ≥65 years were less likely to receive hypoglycemia-inducing medications, while older patients with comorbidities were more likely. Insurance, but not income, was associated with the use of higher-cost medications.

CONCLUSIONS

Following ADA recommendations, the use of metformin increased, but physicians generally did not individualize treatment according to patients' characteristics. Substantial opportunities exist to improve pharmacologic management of diabetes.

Type 2 diabetes (T2D) affected more than 30 million U.S. adults in 2015 (1). It is associated with serious complications, higher mortality, and enormous costs (2). In addition to lifestyle measures, pharmacologic management of T2D is important to maintain glycemic control and prevent complications. Through the 1990s, a limited

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Received 2 December 2019 and accepted 6 March 2020

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-2424/-/DC1.

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This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

number of diabetes medications were available, including metformin, sulfonylureas, thiazolidinediones (TZDs), and insulin. These agents reduce HbA_{1c} by 0.5–1.5%. Some cause hypoglycemia and weight gain (3). Since 2000, six additional classes of medications have been approved. They all reduce HbA_{1c} with minimal hypoglycemia and/or weight gain, and at least two classes have agents within them that can reduce cardiovascular events and all-cause mortality (4–7). However, these newer medications are between 50- and 200-fold more expensive than older generic medications (4).

With the intent to improve care for patients with diabetes, the American Diabetes Association (ADA) has published *Standards of Medical Care in Diabetes* since 1988. Updated at least annually, the ADA's Standards of Care outline options for screening, diagnosis, and treatment. The ADA offered no specific drug recommendations until 2007, when they recommended metformin as first-line therapy, with insulin, TZDs, and sulfonylureas as add-on therapies (8). Since 2012, the ADA has endorsed a patient-centered approach that emphasizes individualization of glycemic targets and drug therapies. Metformin is still recommended first, but the selection of second-line drugs requires balancing efficacy, hypoglycemia risk, weight impact, and cost (9). In 2018, in light of multiple cardiovascular outcome trials, sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RA) were recommended for patients with cardiovascular disease (CVD) in conjunction with lifestyle management and metformin. Recommendations for the use of SGLT2i and GLP-1 RA in patients with heart failure and chronic kidney disease were added in 2019 (10).

High prices have limited access to new drugs (11), and the proliferation of medication classes has complicated prescribing decisions. Little is known about the trends in overall use or the prescribing of specific medications, or how they are distributed among the population. It is also not known to what extent physicians individualize treatment. Using population-level survey data, we examined temporal trends in pharmacologic management for T2D overall and by drug class. We also investigated whether diabetes treatments were individualized by examining medication prescription by hypoglycemia risk, weight effects, cardiovascular benefit, and cost. We hypothesized that *1*) treatment would increase over time, *2*) patients at high risk for hypoglycemia would be less likely to receive drugs causing hypoglycemia, *3*) obese patients would be less likely to receive drugs that promote weight gain and more likely to receive drugs that promote weight-loss, and *4*) patients with low income or no insurance would be less likely to receive high-cost medications. As an analysis of interest based on recently available cardiovascular outcome trials, we also hypothesized that patients with CVD would be more likely to receive drugs with cardiovascular benefit. Understanding the prescribing patterns of diabetes medications and the implementation of individualized treatment for T2D can inform clinical practice and identify areas for improvement.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

We conducted a retrospective, cross-sectional analysis of National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2016. Because the data are de-identified, our study was exempted by the Cleveland Clinic Institutional Review Board. We included people aged ≥18 years who had ever been told they had diabetes, had an HbA_{1c} >6.4%, or had a fasting plasma glucose >125 mg/dL. We excluded pregnant women and patients with probable type 1 diabetes (T1D), defined as those aged <20 years receiving only insulin (12). Fasting plasma glucose was calibrated to adjust for changes in laboratory methods and equipment across years.

Outcome Measure

Use of medications in the 30 days prior to the interview was ascertained from self-report, and interviewers reviewed drug containers. We calculated the prevalence of patients taking zero, one, two, and three or more diabetes drugs. Trends in use were estimated for the ADA's seven preferred classes: metformin, sulfonylureas, TZDs, dipeptidyl peptidase 4 inhibitors (DPP-4i), GLP-1 RA, SGLT2i, and insulin. We categorized sulfonylureas, meglitinides, and insulin as medications causing hypoglycemia and others as not. On the basis of clinical trial and observational studies (13,14), we identified patients at risk for hypoglycemia by age (≥65 years), HbA_{1c} (<6%), or both. Because there is no established age or HbA_{1c} threshold to be considered high risk (14,15), we performed a sensitivity analysis using age ≥75 years and HbA_{1c} <7%. We also defined high risk based on the presence of comorbid conditions that increase the risk or harms of hypoglycemia: heart failure, CVD, cancer, liver disease, chronic kidney disease, cognitive impairment, or functional dependence. We classified sulfonylureas, TZDs, meglitinides, and insulins as causing weight gain; SGLT2i, GLP-1 RA, and pramlintide as promoting weight loss; and others as weight neutral (10). Obesity was defined as a BMI of ≥30 kg/m^2. Drugs with cardiovascular benefit included canagliflozin, empagliflozin, and liraglutide (10). We excluded exenatide, semaglutide, and dapagliflozin because NHANES did not distinguish between exenatide extended release and its other forms (only the extended-release formulation has CVD benefit), while data on semaglutide and dapagliflozin were available only very recently (10). Patients were considered to have CVD if they had ever been told they had coronary heart disease, angina pectoris, heart attack, or stroke. Finally, we categorized drugs by cost. Human regular, NPH, and premixed NPH/regular 70/30 insulin were considered low cost, and insulin analogs were considered high cost. For noninsulin therapies, we considered any diabetes medications that had at least one generic version approved by the U.S. Food and Drug Administration in a survey cycle (16) as low cost and all others as high cost (Supplementary Table 1). Patients with an income-to-poverty ratio of <1 were considered low-income patients, and those without any type of private or public insurance were considered uninsured.

Statistical Analysis

Descriptive statistics of patient characteristics were assessed for the combined two most recent survey cycles during 2013–2016. Logistic regression was used to assess the significance of trends over time with the midpoint of each survey cycle as a continuous independent variable. A two-sided *P* value of <0.05 was considered significant. Use by drug classes was estimated for each 2-year cycle from 2003 to 2016, with monotherapy and combination therapy estimated separately. If patients used a combination drug, both ingredients were counted. Therefore, the proportions of use among

patients with combination therapy can add up to more than 100%. For the analyses of use by hypoglycemia risk, weight effect, cardiovascular benefit, and cost, we included only treated patients and excluded those receiving only metformin because the recommendation for individualized treatment did not apply. We compared the prevalence of use among patient subgroups with specific characteristics. For patients at risk for hypoglycemia, we also compared their achieved HbA_{1c} versus others to test whether physicians individualized treatment targets. Because the evidence of cardiovascular benefit is relatively new, the analysis of medications with cardiovascular benefit was limited to the 2015–2016 survey cycle, while other analyses used aggregated 2013–2016 data. The recommendation for heart failure and chronic kidney disease was added in 2019; hence, we did not assess this indication. All analyses were conducted using Stata 14.2 (College Station, TX) and accounted for the complex survey design of NHANES.

RESULTS

The response rate by cycle ranged from 61% to 80%. Between 59% and 77% of participants completed health examinations. Interviewers observed containers for 78–95% of prescription drugs. The combined sample included 6,323 patients with diabetes, representing 26.5 million patients. There were no significant differences in mean age, sex, race, or BMI across survey years. However, mean HbA_{1c} increased significantly from 7.1% in 2003–2004 to 7.3% in 2015–2016. The increase was limited to patients treated with two drugs or more (Supplementary Table 2). The proportion of patients with $HbA_{1c} \geq 7\%$ increased from 39% to 45% ($P = 0.01$).

Overall Medication Use and by Drug Class

Table 1 shows the prevalence of patients with diabetes taking one or more and three or more diabetes medications in 2013–2016. Of the patients, 67% received at least one medication, and 11% took three or more. Older age (≥45 years), having health insurance, being white, and having an $HbA_{1c} \geq 7\%$ were associated with taking medication ($P < 0.05$). From 2003 to 2016, pharmacologic treatment increased ($P < 0.001$), primarily monotherapy (Fig. 1). Treatment with any medication increased significantly among patients with $HbA_{1c} \geq 7\%$ but not below (Supplementary Fig. 1).

Metformin as First-Line Therapy

Among patients on monotherapy, the use of metformin increased from 33% in 2003–2004 to 74% in 2015–2016 ($P < 0.001$) (Fig. 2*A*). Over the same period, sulfonylurea monotherapy decreased from 33% to 8%. Insulin monotherapy also decreased, but the change was not significant. Other classes were rarely used as monotherapy. Among patients using combination therapy, metformin was the most common agent, but its use plateaued at 70% in 2003–2004. In 2015–2016, sulfonylureas and insulin were both used by 50% of patients, but use was trending in opposite directions with sulfonylurea use declining and insulin use increasing. One-fifth of patients received a DPP-4. The use of TZDs fell to 4% (Fig. 2*B*). The increase in insulin use was driven entirely by use of insulin analogs, which quadrupled from 2003–2004 to 2015–2016 (Supplementary Fig. 2). Human insulin use declined almost to zero.

Hypoglycemia Risk

Older patients (≥65 years) who were treated with any medication had lower HbA_{1c} values than younger patients (7.1% vs. 7.7%, $P < 0.001$), and they had similar HbA_{1c} regardless of the presence of comorbidities. Use of drugs potentially causing hypoglycemia did not differ by age. In contrast, fewer patients with lower HbA_{1c} (<7%) were prescribed a hypoglycemia-inducing drug compared with patients with higher HbA_{1c}. In multivariable analysis, patients with low HbA_{1c} had a significantly lower odds of receiving such drugs than those with high HbA_{1c}, while older patients had the same odds as younger patients (Table 2). Patients aged ≥75 years with $HbA_{1c} < 7\%$ were not less likely to receive hypoglycemia-inducing drugs, and older patients with comorbidities were actually more likely to receive them than those without.

Weight Impact

Overall, 86% of patients received a weight-neutral drug regardless of obesity status. While half of obese patients received at least one drug causing weight gain, only 9% received a drug that promoted weight loss other than metformin. Compared with nonobese patients, obese patients were as likely to receive drugs causing weight gain (adjusted odds ratio [OR] 1.21; 95% CI 0.81–1.78) as those promoting weight loss (adjusted OR 1.29; 95% CI 0.51–3.23).

Cardiovascular Benefit

In 2015–2016, 21% of patients with T2D had known CVD. Overall, 6% of patients received drugs with cardiovascular benefit (10% of patients with CVD and 5% of patients without). The adjusted OR for patients having CVD versus not was 2.78 (95% CI 0.66–11.74).

Cost

Use of high-cost drugs by uninsured patients was less than half that among patients with insurance (12% versus 25%, $P = 0.03$). In contrast, use of high-cost drugs did not differ by income: 24% for patients with an income-to-poverty ratio of <1 versus 26% for a ratio ≥4 (P value = 0.56). In multivariable analysis, use of any high-cost diabetes medications was significantly associated with higher HbA_{1c}, severe obesity (BMI ≥35 kg/m^2), and having health insurance (Supplementary Table 3).

CONCLUSIONS

In this cross-sectional study, we used data from NHANES to examine trends in diabetes medication prescribing and to assess whether physicians followed ADA recommendations to individualize treatment based on hypoglycemia risk, weight effect, cardiovascular benefit, and cost. Of note, the ADA's recommendation on drugs with cardiovascular benefit was not made until 2018. We found that from 2003 to 2016, more patients received pharmacologic therapy, primarily monotherapy with metformin. Use of any medication increased significantly for patients with $HbA_{1c} \geq 7\%$, but overall control of diabetes worsened, with HbA_{1c} increasing each year.

In accordance with the ADA's 2007 standards of medical care, use of metformin as monotherapy increased from 33% to 74%, while use of other medications as monotherapy declined substantially. Among patients receiving combination therapy, metformin use has not increased since 2003–2004 but remains high at 70%. Decline in the use of sulfonylureas, both as monotherapy and as second-line therapy, may be because of their side effect profile, including weight gain and hypoglycemia, compared with other classes of diabetes medications (10). The low price of sulfonylureas likely contributed to their persistence, as there is essentially no advertising or detailing for them. TZD use also declined sharply after peaking in 2006. Concerns about adverse cardiovascular

Table 1—Prevalence of diabetes drug use among U.S. adults with T2D, 2013–2016

		Any diabetes medications		Three or more diabetes medications	
	Number of participants	% (95% CI)	*P* value	% (95% CI)	*P* value
Overall	1,991	67 (65–70)		11 (10–13)	
Mean HbA_{1c}, %	1,894	7.5 (7.4–7.6)		8.1 (7.8–8.3)	
HbA_{1c} ≥7%					
Yes	907	81 (78–84)	**<0.001**	19 (16–22)	**<0.001**
No	987	55 (51–59)		4 (3–6)	
Age-group, years					
18–44	266	48 (41–56)	**<0.001**	9 (5–15)	0.470
45–64	866	67 (63–72)		12 (9–15)	
≥65	859	75 (70–78)		11 (9–13)	
Sex					
Female	950	67 (62–70)	0.672	10 (7–12)	0.156
Male	1,041	68 (64–71)		12 (10–15)	
Race/ethnicity					
Non-Hispanic white	611	70 (66–74)	**0.017**	12 (9–15)	0.685
Non-Hispanic black	488	66 (61–72)		10 (7–13)	
Hispanic	637	60 (56–64)		11 (8–14)	
Other	255	63 (53–71)		10 (7–14)	
Education					
<High school	641	66 (59–73)	0.859	10 (8–13)	0.156
High school graduate/GED	469	66 (61–71)		10 (7–13)	
Some college	547	67 (62–72)		10 (7–13)	
College graduate and above	330	69 (61–76)		15 (10–22)	
Family income-to-poverty ratio					
<1	489	62 (57–68)	0.095	9 (7–13)	0.277
1 to <2	503	63 (58–67)		9 (6–12)	
2 to <4	482	69 (64–74)		13 (9–18)	
≥4	320	70 (63–76)		13 (9–19)	
Insurance status					
Any private	890	69 (65–72)	**<0.001**	12 (10–16)	**0.018**
No insurance	253	48 (42–55)		3 (1–5)	
Government only	835	70 (66–74)		11 (9–14)	
BMI					
<25 kg/m^2	256	61 (53–70)	0.544	8 (5–11)	**0.026**
25 to <30 kg/m^2	554	66 (60–72)		8 (6–11)	
30 to <35 kg/m^2	529	69 (63–74)		12 (9–15)	
≥35 kg/m^2	560	68 (64–72)		14 (11–17)	

Boldface type indicates statistical significance. GED, General Education Diploma.

events of rosiglitazone, increasing recognition of the risk of heart failure that was confirmed in a meta-analysis in 2007, an additional black box warning for bladder cancer in 2011, and risk of fractures may have caused it to lose popularity among physicians (17–20). In addition, the U.S. Food and Drug Administration's prescribing and dispensing restrictions for rosiglitazone from 2010 to 2013 and the loss of pioglitazone's patent in 2011 could have caused manufacturers to stop marketing TZDs. Because pioglitazone is now recommended for the treatment of nonalcoholic steatohepatitis and fibrosis (21), which affect ~60% of patients with T2D (22), it may be time to reconsider its use. Dramatic increases in insulin use were limited to expensive analogs. Reasons for the decline in the use of human and NPH insulin are unclear. Analogs have been promoted heavily by manufacturers and by ADA as safer in T1D (10). In patients with T2D, analogs may be perceived to be more effective because they are less variable and cause less nocturnal hypoglycemia (23,24). Hence, it has been argued that analogs are easier to use, improving treatment adherence and satisfaction (25). In practice, however, newer insulins have benefit and risk profiles similar to those of human insulin for T2D (26–28) despite being 5–15 times more expensive (29). As noted in the most recent ADA Standards of Care, the out-of-pocket cost of analogs can lead to treatment nonadherence, and human insulin may be appropriate for many patients (4).

It generally takes almost two decades for research evidence to be translated into clinical practice (30), and adherence to clinical guidelines is often poor (31). Our study appears to be the first to examine whether physicians follow the ADA's new Standards of Care by considering medication side effect profiles to individualize treatment. While some patients at risk for hypoglycemia (those with low HbA_{1c}) were less likely to receive drugs that cause hypoglycemia, older patients were not. Moreover, HbA_{1c} targets were not relaxed for older patients or those with comorbidities, and the most vulnerable group (age ≥65 years with comorbidities) was significantly more likely to receive hypoglycemia-causing drugs.

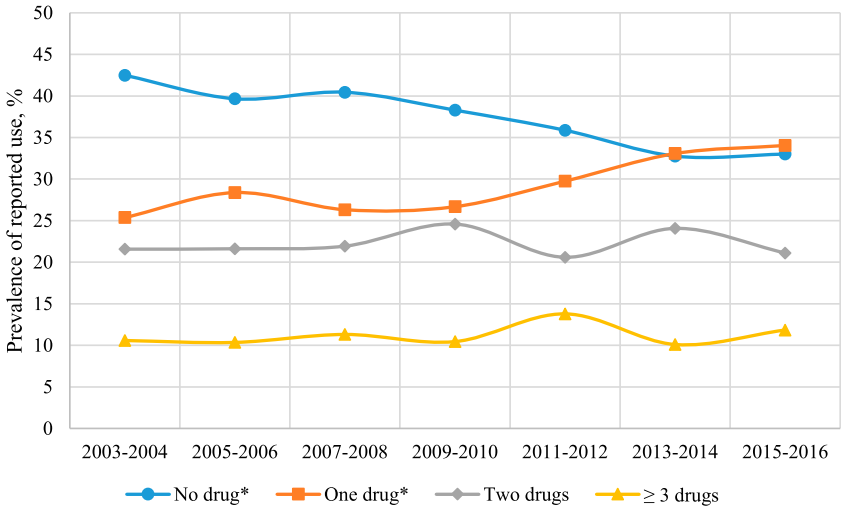

Figure 1—Trends of diabetes drug use by the number of drugs among U.S. adults with T2D, 2003–2016. *P values for trend <0.05.

Because 38% of all T2D patients are ≥65 years of age, these findings have widespread application.

Presently, 88% of patients with T2D are either overweight or obese (1). We found that obese and nonobese patients were equally likely to have taken drugs that promoted weight gain. Drugs causing weight gain were prescribed five times more often than drugs that promoted weight loss, potentially worsening insulin resistance despite lowering glucose levels. Only 10% of patients with a history of CVD were prescribed canagliflozin, empagliflozin, or liraglutide, but these drugs were relatively new and expensive. In addition, canagliflozin carries an increased risk of amputation (32). Data on cardiovascular benefits were not available until 2015, and the ADA's recommendation was not made until 2018. Even so, our findings suggest that attention should be paid to their uptake in people who can benefit most.

A number of studies have examined the trends in diabetes treatment in various populations, and our findings are generally consistent with theirs. From 1997 to 2000, the use of insulin decreased when physicians turned to new oral medications (metformin, new sulfonylureas, and TZDs) (33). Since then, metformin use has continued to increase, but prescriptions for sulfonylureas and TZDs have declined, being replaced by newer, more expensive drugs (34). After a decline in the late 1990s, the use of insulin recovered to become the third most prescribed drug by 2013, due primarily to the increase in basal analogs (35). Other new agents—DPP-4 inhibitors and GLP-1 RA—also increased consistently (35). A more recent study, using electronic medical records, reported trends similar to ours in monotherapy but not in combination therapy. That study reported that DPP-4 inhibitors were prescribed more often than insulin (36). However, the study lacked reliable information on whether prescriptions were filled and had an overrepresentation of sicker and insured populations, which might account for the differences (36). An earlier study using 1999–2012 NHANES data found that diabetes medication use was increasing; however, only four drug classes were reported, and patient factors were not examined (37). Most recently, Landon et al. (38) reported a similar ranking of use by drug class in a Medicare population despite potential difference in diabetes management practices for older patients. Our study appears to be the first population-based analysis that examines the overall pharmacologic treatments for diabetes in the U.S. and the associated

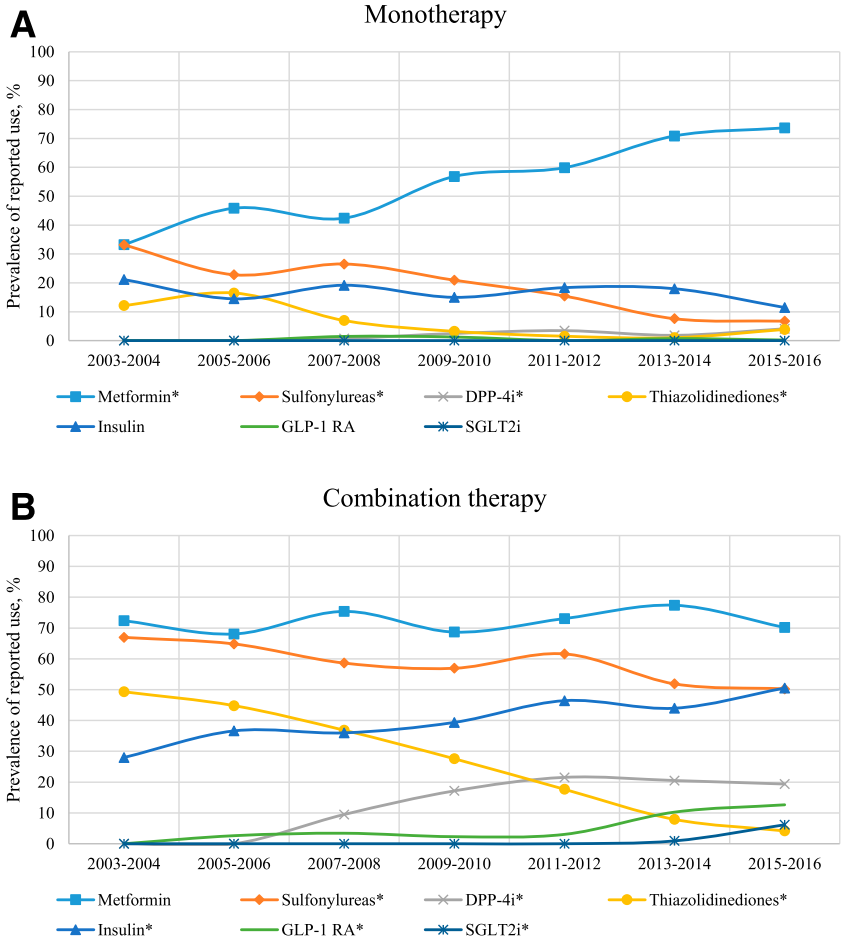

Figure 2—Trends of diabetes drug use by drug class among U.S. adults with T2D who received monotherapy (*A*) and combination therapy (*B*), 2003–2016. *P values for trend <0.05.

Table 2—Prevalence of use and association of patient characteristics and receipt of medications among U.S. adults with T2D, 2013–2016

	Prevalence of use (%) (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Drugs causing hypoglycemia			
Age*			
<65 years	49 (45–54)		
≥65 years	52 (45–58)	1.08 (0.76–1.55)	1.16 (0.77–1.75)
HbA_{1c}*			
≥6%	55 (52–57)		
<6%	16 (9–28)	0.16 (0.08–0.31)	0.18 (0.09–0.36)
Age ≥65 years and HbA_{1c} <6%*			
No	52 (49–55)		
Yes	14 (6–29)	0.14 (0.06–0.37)	0.17 (0.06–0.44)
Among patients aged ≥65 years¥			
Without comorbidity¥	41 (36–47)		
With comorbidity	56 (51–61)	1.81 (1.26–2.59)	2.94 (1.56–5.58)
Sensitivity analysis for drugs causing hypoglycemia*			
Age			
<75 years	49 (46–53)		
≥75 years	57 (48–65)	1.34 (0.89–2.01)	1.48 (0.91–2.40)
HbA_{1c}			
≥7%	69 (65–73)		
<7%	27 (21–33)	0.16 (0.11–0.23)	0.15 (0.10–0.23)
Age ≥75 years and HbA_{1c} <7%			
No	51 (48–54)		
Yes	41 (29–55)	0.67 (0.39–1.16)	0.70 (0.40–1.2)
Drugs causing weight gain†			
BMI <30 kg/m^2	50 (44–56)		
BMI ≥30 kg/m^2	52 (46–57)	1.08 (0.75–1.57)	1.21 (0.81–1.78)
Drugs promoting weight loss†			
BMI <30 kg/m^2	6 (3–12)		
BMI ≥30 kg/m^2	9 (7–13)	1.60 (0.71–3.59)	1.29 (0.51–3.23)
Drugs with cardiovascular benefit‡			
No CVD	5 (2–10)		
CVD	10 (4–22)	2.20 (0.53–9.14)	2.78 (0.66–11.74)

*Adjusted for sex, race, education, income, insurance, and BMI. ¥Adjusted for sex, race, education, income, insurance, BMI, and HbA_{1c}. †Adjusted for age, sex, race, education, income, insurance, and HbA_{1c}. ‡Adjusted for age, sex, race, education, income, insurance, BMI, and HbA_{1c}. ¥Comorbidity includes heart failure, CVD, cancer, liver disease, chronic kidney disease, cognitive impairment, or functional dependence.

patient factors and that includes patients without insurance. In addition to being demographically representative at the national level, NHANES has a high response rate, with most drugs confirmed by visual inspection. It also contains measures of HbA_{1c} and fasting glucose, which enhanced the robustness of case finding.

Our study has some important limitations. Although we stratified medication use by cost based on approval date for generics, we could not tell how many patients actually used generic versions. However, most insurance plans require prior authorization for brand-name medications, and most patients quickly transition to generics once available. NHANES data also does not distinguish between T1D and T2D, so our study likely included some patients with T1D. However, because >95% of patients with diabetes have T2D (10), drug use in a small proportion of patients with T1D would not affect our findings substantially. NHANES prescription medication data were available only through 2015–2016; thus, we could not assess the ADA's most recent recommendation regarding patients with chronic kidney disease. Finally, because NHANES data are cross-sectional, we could not tell if the drugs used were newly filled, if patients had switched medications, or the order in which drugs were initiated for patients using combination therapy.

In conclusion, pharmacologic treatment for T2D increased from 2003 to 2016. In accordance with the ADA's Standards of Care, metformin was the most frequently prescribed first-line therapy, while the use of sulfonylureas and TZD decreased. The use of insulin increased throughout the study period, with insulin analogs displacing human insulins almost entirely. More than 50% of patients aged ≥65 years still received drugs that cause hypoglycemia, and there was little evidence that doctors tailored treatment for patients with obesity or CVD as recommended by the ADA. This study identified the current baseline to which new guidelines will be applied and demonstrated substantial opportunity for improvement.

Funding. A.D.M.-H. receives funding from the Agency for Healthcare Research and Quality, grant K08HS024128.

Duality of Interest. A.D.M.-H. has received research funding from Novo Nordisk and Merck not related to the current study. W.H.H. serves on a Data Safety Monitoring Board for Merck Sharp & Dohme. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.L. was responsible for study concept and design, analyzed and interpreted data, and wrote the manuscript. A.C. acquired data. M.B.R. supervised the study. All authors interpreted data and reviewed and edited the manuscript. M.B.R. and P.L.

are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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