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ORIGINAL ARTICLE

Clinical Trials and Investigations

Use and continuity of weight-modifying medications among adults with diabetes and overweight/obesity: US population study

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Abstract

Objective: Trends in use and continuity of use of diabetes-specific and non-diabetes weight-reducing (WR), weight-inducing (WI), and weight-neutral (WN) medications were examined among US adults with diabetes and overweight/obesity.

Methods: Serial cross-sectional data from Medical Expenditure Panel Surveys (2010–2019) for adults (≥18 years) with diabetes and BMI ≥27 kg/m^2 (≥25 kg/m^2 for Asians) were analyzed.

Results: Among 7402 US adults with diabetes and overweight/obesity (mean age 60.0 years [SD 13], 50% female), 64.9% of participants used any WI medications, decreasing from 68.9% (95% CI: 64.3%–73.5%) in 2010 to 58.6% (95% CI: 54.7%–62.5%) in 2019. It was estimated that 13.5% used WR medications, increasing 3.31-fold, from 6.4% (95% CI: 4.1%–8.7%) to 21.2% (95% CI: 18.0%–24.4%) and that 73.1% used WN medications, ranging from 70.5% (95% CI: 66.5–74.6) to 75.0% (95% CI: 71.7%–78.4%). Among adults using diabetes-specific WI (53.7%), WR (7.1%), and WN (62.4%) medications during the first year, 7.3%, 16.4%, and 9.0% discontinued it in the second year, respectively.

Conclusions: Over 2010–2019, 64.9% of adults with diabetes and overweight/obesity were treated with WI medications, 13.5% with WR medications, and 73.1% with WN medications. Discontinuation of WR medications was nearly twice that of WI medications.

INTRODUCTION

In the United States, 37.3 million people have diabetes, which is a major and increasing cause of disability, morbidity, and mortality [1]. Over 95% of people with diabetes have type 2 diabetes (T2D) [2], which often occurs in the setting of excess adiposity. Recent national estimates showed that, among adults with T2D, the prevalence of overweight (body mass index [BMI] ≥25 to 29.9 kg/m^2) decreased from 31.5% to 27.7%, while the prevalence of obesity (BMI ≥ 30 kg/m^2) increased from 51.6% to 62%, from 1999 to 2018 [3]. Obesity is a chronic disease

See Commentary, pg. X.

characterized by excess and ectopic deposition of dysfunctional adipose tissue, and it exacerbates the common complications and comorbidities of diabetes, including hypertension, hyperlipidemia, cardiovascular disease, non-alcoholic fatty liver disease, sleep apnea, and osteoarthritis [4–6]. Addressing obesity is therefore a core component of diabetes management and for improving health outcomes [7].

Recent advances in the pharmacological management of diabetes [8, 9] have shifted diabetes care away from focusing solely on glycemic control to also reducing the risk of complications and optimizing weight management. Among several classes of glucose-lowering medications for T2D, only two have demonstrated meaningful weight loss (i.e., glucagon-like peptide-1 [GLP-1] receptor agonists and sodium-glucose co-transporter [SGLT] inhibitors). Consequently, clinical guidelines have recommended their preferential use in patients with overweight or obesity [5, 10, 11]. Importantly, some classes of glucose-lowering medications result in weight gain (sulfonylureas, thiazolinediones, insulin) and should not be used preferentially in patients with excess adiposity. Other agents, such as metformin and dipeptidyl-peptidase-4 inhibitors, do not increase weight gain and may induce modest weight loss (<2 kg), but not to the extent needed to prevent obesity-related complications [5, 10–12], and thus are considered weight-neutral (WN). Additionally, there are few non-diabetes medications approved specifically for weight loss that are recommended for all patients with BMI ≥ 30 kg/m^2 or with BMI ≥ 27 kg/m^2 in the setting of coexisting obesity-related complications such as diabetes [5, 10, 11].

Prior studies have shown that fewer than 5% of patients meeting evidence-based criteria for obesity pharmacotherapy are treated with antiobesity drugs [13–15]. However, there are limited nationally representative studies examining the treatment patterns of people with diabetes and overweight or obesity, and there are no studies examining both diabetes-specific and non-diabetes weight-inducing (WI), WN, and weight-reducing (WR) medications. This is of particular significance given the stagnation in achievement of diabetes care goals in the past decade [3]. We analyzed nationally representative data to estimate trends in prevalence of medication use and continuity of use of WR, WN, and WI medications in adults with diabetes and overweight/obesity (meeting criteria for pharmacological treatment of obesity), from 2010 to 2019.

Study Importance

What is already known?

- Guidelines recommend preferentially using weight-reducing medications in adults with diabetes and overweight/obesity.

What does this study add?

- In this US nationwide study from 2010 to 2019, we estimated use trends of diabetes-specific and non-diabetes weight-reducing, weight-inducing, and weight-neutral medications.
- Up to 64.9% of US adults with diabetes and overweight/obesity received weight-inducing medications, whereas only 13.5% received weight-reducing medications.

How might these results change the direction of research or the focus of clinical practice?

- Our findings may inform scientific societies, clinicians, advocacy groups, and policymakers to align prescribing and access with guidelines.

METHODS

We used data from the Medical Expenditure Panel Survey (MEPS) sponsored by the Agency for Healthcare Research and Quality (https://meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp). This study was deemed IRB exempt as it involved analysis of de-identified publicly available data. Study results are reported in accordance with STROBE guidelines [16]. To analyze national trends in medication use, we used MEPS's serial cross-sectional data regarding prescribed medicines, and we used a combination search for the active ingredient/generic name available in MEPS and linked Food and Drug Administration unique national drug codes. For continuity of medication use, we used MEPS's longitudinal data files for each participant over their 2 years of follow-up.

We included adults (≥18 years) with diabetes and BMI ≥ 27 kg/m^2 (≥25 for Asian participants) or having an obesity-related ICD code (ICD-9-CM: 278.xx or ICD-10-CM: E66.xx) from January 1, 2010, to December 31, 2019. Adults with missing age, diabetes diagnosis, BMI data (self-reported), or who missed ≥1 round of interviews were excluded (see Supplementary Figure S1).

Drug class definitions

Medications were stratified into two classes as: (1) "diabetes-specific" or "non-diabetes medications". Further, medications were sub-stratified as "WI, WR, WN"; by (2) their clinically meaningful weight effects (of at least 2-kg change from baseline), as (1) endorsed by clinical practice guidelines [10, 12, 17–19] and (2) confirmed in systematic reviews [10, 12, 17, 18]. The complete list of medications within each group is available in Tables S1 and S2.

Outcomes

The outcomes of interest were the prevalence, prescription fills, and continued use of each medication category and specific medications among adults with diabetes and overweight or obesity. Prevalence (use per 100 person-years) of weight-modifying medications was defined as the number of respondents reporting any weight-

TABLE 1 Characteristics of US adults with diabetes and overweight/obesity: 2010–2019

Characteristic	2010–2011	2011–2012	2012–2013	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018	2018–2019	Overall
Diabetes and overweight/obesity (unweighted *n*)	675	870	806	853	809	852	917	791	829	7402
Mean age, y	57.5	60.8	60.0	60.9	59.9	59.9	60.2	59.9	60.5	60.0
SD	13.3	12.5	13.4	13.4	12.5	13.3	12.1	12.7	13.3	13.0
Sex, female (%)	48.9	49.1	50.3	50.5	52.3	49.4	49.3	48.8	50.6	50.0
Race (%)										
Black, non-Hispanic	17.3	17.0	15.8	15.0	15.9	17.7	14.1	16.4	14.0	15.9
White, non-Hispanic	61.7	62.3	61.9	64.7	60.0	61.1	60.9	62.7	64.1	62.1
Hispanic	14.9	15.4	14.9	13.0	15.8	13.4	17.2	14.3	13.3	14.7
Asian	3.4	3.1	4.2	3.8	4.4	3.7	5.3	3.3	4.5	4.0
Other	2.8	2.2	3.2	3.5	3.9	4.2	2.5	3.3	4.2	3.3
Insurance (%)										
Medicaid	6.8	6.9	8.2	6.3	8.0	6.7	8.5	9.5	8.7	7.8
Medicare	33.1	44.5	46.3	45.5	47.4	42.8	44.4	46.3	48.4	44.3
Private	43.3	34.1	35.1	33.9	33.9	38.1	37.8	34.8	36.5	36.4
Uninsured	9.9	8.6	6.7	7.8	5.8	5.1	4.1	2.7	1.7	5.7
Other	6.9	5.9	3.6	6.5	4.9	7.4	5.2	6.6	4.7	5.8
Poverty category[b] (%)										
<100% FPL	14.9	20.2	15.1	13.9	16.1	12.2	14.6	14.5	12.8	14.8
100%–125% FPL	4.5	5.0	5.9	4.9	5.6	4.7	6.2	7.4	5.3	5.5
125%–200% FPL	13.5	15.3	16.6	15.9	13.9	15.7	17.4	16.7	15.4	15.6
200% to <400% FPL	34.7	30.8	30.8	35.7	28.5	31.0	27.2	26.1	30.2	30.5
>400% FPL	32.3	28.6	31.6	29.6	35.9	36.5	34.6	35.3	36.2	33.5
BMI category, kg/m^2 (%)										
25–26.9[a]	0.9	1.0	1.7	1.5	1.8	0.9	1.5	0.3	2.0	1.3
>27–29.9	23.6	25.0	27.2	29.3	23.7	26.9	25.3	25.1	25.2	25.7
30–34.9	35.8	36.7	35.2	32.9	36.9	33.3	36.2	33.3	33.1	34.9
35–39.9	21.5	20.6	17.8	20.2	21.4	22.6	20.5	23.5	21.0	21.0
>40	18.2	16.7	17.7	16.1	16.2	16.3	16.5	17.8	18.7	17.1

Note: Data presented as *N* (%), except when noted otherwise. Continuous variables are reported as mean (SD), and categorical variables are reported as proportions.

[a]Weight-reducing prescriptions are guideline recommended for (1) adults with BMI ≥ 25 kg/m^2 for Asian Adults or (2) BMI ≥ 27 kg/m^2 for all other adults. Our final sample reflects participants with complete longitudinal data.

[b]Percentage yearly income compared to federal poverty level (FPL). Estimates were generated using Medical Expenditure Panel Survey data from 2010 to 2019 and adjusted for complex survey design to generate nationally representative estimates.

modifying medication use (defined as ≥2 fills within a year) for the numerator and the study population (adults with diabetes and BMI ≥ 25 [for Asian subpopulations] or 27 kg/m^2 [all other racial and ethnic groups]) as the denominator by each year-cycle. Continuity of medication use was defined as the proportion of adults with diabetes and overweight/obesity who used each drug group in their second year out of those using the medication in their first year.

Statistical methods

We calculated period (2010–2019) and annual prevalence of medication use, the number of unique prescription fills, and continuity of medication use. Estimates were adjusted for the complex survey design to generate nationally representative estimates. We calculated adjusted prevalence for each subgroup using quasibinomial logistic regression models with an outcome of medication use and independent variables for age, sex, and race and ethnicity.

Medication use was examined for specific sub-cohorts by stratifying adults with diabetes and overweight/obesity by key co-variates: race and ethnicity, insurance, and BMI groups. Race and ethnicity use values were age- and sex-adjusted; insurance values were sex- and race-adjusted due to collinearity with the age variables; and BMI values were age-, sex-, and race-adjusted.

We separately calculated multivariate logistic regression models to simultaneously examine associations among covariates of age, sex, race

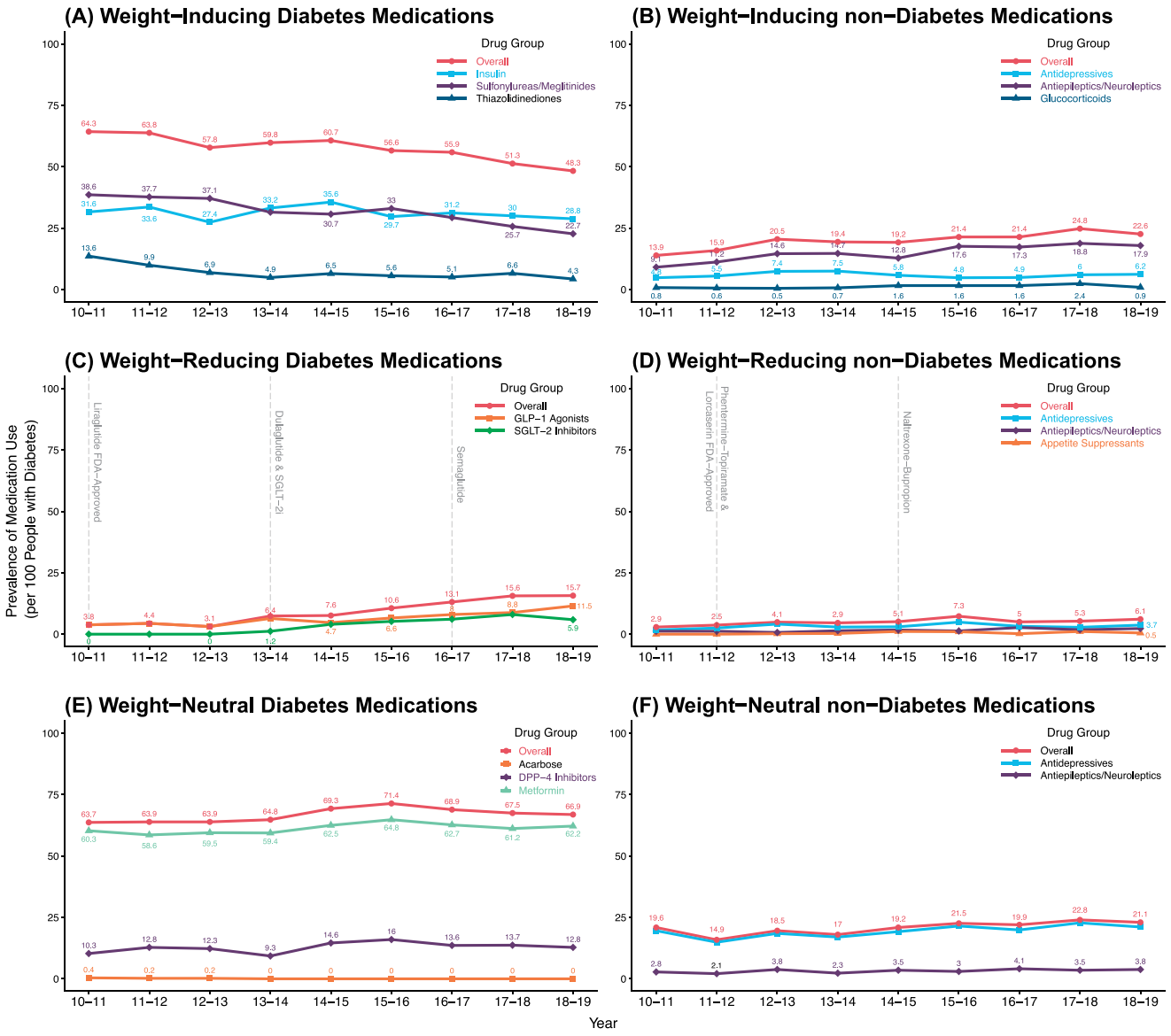

FIGURE 1 Trends in use of weight-modifying medications among US adults with diabetes and overweight/obesity by type of medication, from 2010 to 2019: (A) weight-inducing diabetes medications, (B) weight-inducing non-diabetes medications, (C) weight-reducing diabetes medications, (D) weight-reducing non-diabetes medications, (E) weight-neutral diabetes medications, and (F) weight-neutral non-diabetes medications. Medical Expenditure Panel Survey (MEPS) Longitudinal Data and Prescription Medicines Data. Estimates were adjusted for complex survey design to generate nationally representative estimates of medication use. Medication use was defined per participant as ≥2 medication fills over the 2-year longitudinal period. MEPS uses an overlapping panel design, and participants are enrolled in a staggered 2-year panel. We report medication use by the years corresponding to each panel. Dashed lines indicate Federal Drug Administration approval dates for medications. [Color figure can be viewed at wileyonlinelibrary.com]

and ethnicity, BMI category, insurance, pooled year panels, and use of a weight-modifying medication. We assessed collinearity between variables using a correlation matrix and calculated the variation inflation factor between age and insurance variables and found no evidence for high collinearity. We generated a forest plot populated by category-specific odds ratios for each weight-modifying medication group.

We calculated mean and standard deviations for continuous variables and proportions and calculated 95% confidence intervals for categorical variables. We also reported percentage change and 95% confidence intervals in use estimates from 2010 to 2019. All analyses were performed using R version 4.0. We calculated standard errors and variance for survey-weighted estimates using Taylor Series Linearization methodology provided in the Survey package. Plots were generated using the ggplot2 package (see Supplementary materials).

RESULTS

From 2010 to 2019, we identified 11,058 adult participants in MEPS with diabetes. Of those, we identified 7402 adults with diabetes and

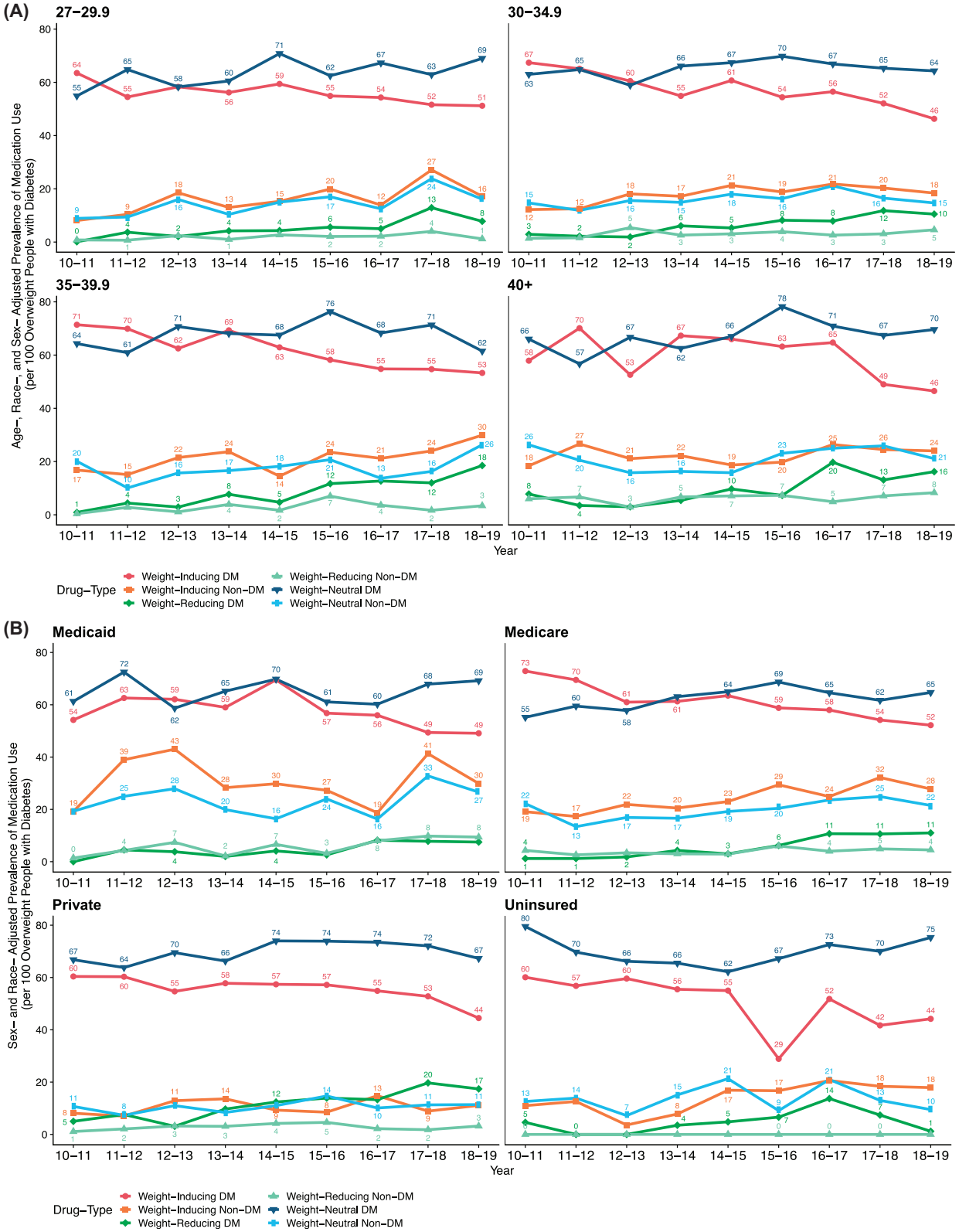

FIGURE 2 Trends in use of weight-modifying medications among US adults with diabetes and overweight/obesity, from 2010 to 2019: (A) BMI (age-, sex-, and race-adjusted), (B) insurance (sex- and race-adjusted), and (C) race and ethnicity (age- and insurance-adjusted). Medical Expenditure Panel Survey (MEPS) Longitudinal Data and Prescription Medicines Data. Estimates were adjusted for complex survey design to generate nationally representative estimates of medication use. Medication use was defined per participant as ≥2 medication fills over the 2-year longitudinal period. MEPS uses an overlapping panel design, and participants are enrolled in a staggered 2-year panel. We report medication use by the years corresponding to each panel. BMI values were age-, sex-, and race-adjusted; race and ethnicity use values were age- and sex-adjusted; and insurance values were sex- and race-adjusted due to collinearity with the age variables. [Color figure can be viewed at wileyonlinelibrary.com]

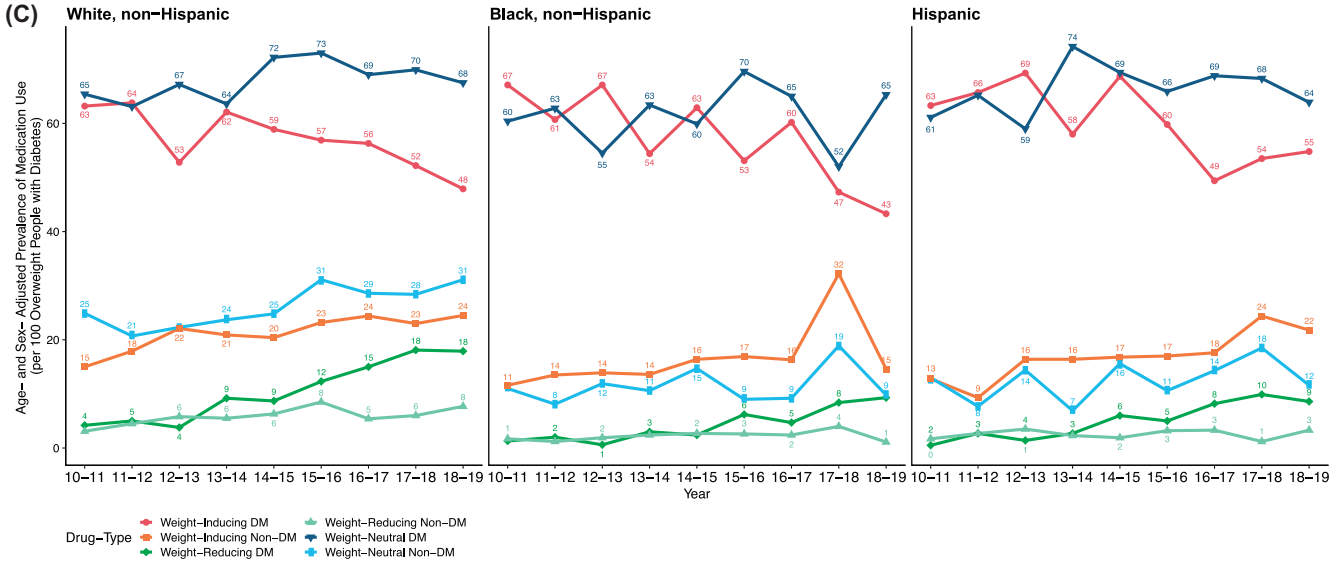

FIGURE 2 (Continued)

overweight or obesity (BMI ≥25.0 [if Asian] and ≥27.0 kg/m^2 [all other races]) and complete data (Supplementary Figure S1). The mean age was 60.0 years (SD 13); 50% were women; 62.1% were Non-Hispanic White, 15.9% were Non-Hispanic Black, and 14.7% were Hispanic (see Table 1). A total of 44.3% of adults with diabetes and overweight or obesity were Medicare beneficiaries, 36.4% had private insurance, 7.8% had Medicaid, and 5.7% were uninsured (see Table 1). On average, the annual number of medication fills was 9.96 per person. Overall, 64.9% of adults with diabetes and overweight or obesity used WI medications, decreasing from 68.9% (95% CI: 64.3%–73.5%) in 2010 to 58.6% (95% CI: 54.7%–62.5%) in 2019 (all values in Supplementary Table S3). However, a total of 13.5% of adults with diabetes and overweight or obesity used any WR medications, increasing 3.31-fold from 6.4% (95% CI: 4.1%–8.7%) in 2010 to 21.2% (95% CI: 18.0%–24.4%) in 2019, and 73.1% used WN medications, ranging from 70.5% (95% CI: 66.5%–74.6%) to 75% (95% CI: 71.7%–78.4%) over the period.

Use of diabetes-specific and non-diabetes weight-modifying (WI, WR, WN) medications

The prevalence of diabetes-specific WI medication (see Figure 1A, all values in Supplementary Table S3) use decreased from 64.3% (95% CI: 59.8%–68.8%) in 2010 to 48.3% (95% CI: 44.4%–52.2%) in 2019. This was driven by a decline in the use of sulfonylureas (38.6% to 22.7%) and thiazolinediones (13.6% to 4.3%) but no change in insulin use (31.6% to 28.8%, see Figure 1A).

Among adults with diabetes and overweight or obesity, non-diabetes WI medication use increased 1.62-fold, from 13.9% (95% CI: 10.8%–17.0%) in 2010 to 22.6% (95% CI: 19.1%–26.1%) in 2019 (see Figure 1B, all values in Supplementary Table S3).

The prevalence of using diabetes-specific WR medications increased 4.13-fold, from 3.8% (95% CI: 1.8%–5.8%) in 2010 to 15.7% (95% CI: 12.6%–18.8%) in 2019 (Figure 1C, all values in Supplementary Table S3). This increase was driven by a significant 3.02-fold increase in use of GLP-1 receptor agonists, from 3.8% (95% CI: 1.8%–5.8%) in 2010 to 11.5% (95% CI: 9.0%–14.0%) in 2019. Use of Sodium-Glucose Loop Cotransporter-2 inhibitors was first observed in 2014 and increased 4.91-fold, from 1.2% (95% CI: 0.4%–2.0%) to 5.9% (95% CI: 3.7%–8.1%).

Meanwhile, the prevalence of non-diabetes WR medications use increased from 2.9% (95% CI: 1.5%–4.3%) in 2010 to 6.1% (95% CI: 3.9%–8.3%) in 2019 (Figure 1D). Use of appetite suppressants (∼<1%) and antiepileptic/neuroleptics (<3%) were generally low and did not change over time.

The use of diabetes-specific WN medications (Figure 1E) did not change over time, from 63.7% (95% CI: 59%–68.4%) in 2010 to 66.9% (95% CI: 63.2%–70.6%) in 2019.

The prevalence of non-diabetes WN medication use increased from 20.9% (95% CI: 17.0%–24.8%) in 2010 to 23.0% (95% CI: 19.9%–26.1%) in 2019 (Figure 1F). This was driven by small increases in antidepressants, from 19.6% (95% CI: 15.9%–23.3%) in 2010 to 21.1% (95% CI: 17.8%–24.4%) in 2019, and antiepileptics from 2.8% (95% CI: 1.2%–4.4%) in 2010 to 3.8% (95% CI: 2.2%–5.4%) in 2019 (all values in Supplementary Table S3).

Adjusted rates (for age, sex, race) of diabetes-specific WI, WR, and WN medication use are shown in Supplementary Tables S4, S5 and S8. Adjusted rates (for age, sex, race) of non-diabetes WI, WR, and WN medication use are shown in Supplementary Tables S6, S7, and S9.

Subgroup/stratified analyses

When stratified by BMI subgroups, the age-, sex-, and race-adjusted trends in use of diabetes-specific WR medications over time was greater for BMI 35 to 39.9 and BMI >40 kg/m^2 (0.9% [95% CI:

0.0%–1.9%] to 18.5% [95% CI: 11.2%–25.8%] and 7.8% [95% CI: 1.9%–13.7%] to 16.2% [95% CI: 9.1%–23.3%], respectively) (Figure 2A, values in Supplementary Table S5/Figure S2). Notably, the adjusted prevalence of use of non-diabetes WR medications was persistently low, ranging from 1% to 4% across BMI groups, except among those with a BMI >40 kg/m^2, for whom prevalence ranged from 6.0% (95% CI: 1.1%–10.9%) in 2010 to 8.3% (95% CI: 4.0%–12.6%) in 2019 (Figure 2A, values in Supplementary Table S7).

When considered as a function of health insurance status, diabetes-specific WR medication use increased most among adults with diabetes and overweight/obesity who were privately insured (5.0% [95% CI: 1.9%–8.1%] in 2010 to 17.4% [95% CI: 12.1%–22.7%] in 2019), while uninsured adults had low use of these medicines (Figure 2B, values in Supplementary Table S5/Figure S3). With respect to diabetes-specific WI medications, there was a decreasing trend among all insurance groups, with the largest decrease among those with private insurance (60.4% [95% CI: 52.6%–68.2%] in 2010 to 44.5% [95% CI: 38.0%–51.0%] in 2019) (Figure 2B, Supplementary Table S4). The use of non-diabetes WI medications was higher and growing among those with Medicaid (19.2% in 2010 to 29.9% in 2019) and lower among those with private insurance (8.1% in 2010 to 11.2% in 2019) (Figure 2B, values in Supplementary Table S6).

Among non-diabetes medications, the adjusted prevalence of WR medications increased the most among those with Medicaid, from 1.4% (95% CI: 0.0%–4.1%) in 2010 to 9.4% (95% CI: 2.9%–15.9%) in 2019, and it remained <5% for those with Medicare and <4% for those with private insurance (Figure 2B, all values in Supplementary Table S7).

Among adults with diabetes and overweight or obesity, the prevalence of diabetes-specific WR medications increased the most among non-Hispanic White individuals (4.2% [95% CI: 1.7%–6.7%] in 2010 to 17.9% [95% CI: 14.0%–21.8%] in 2019) (Figure 2C, Supplementary Table S5/Figure S4). The prevalence of diabetes-specific WI medications declined among Black (67.1% [95% CI: 58.1%–76.1%] in 2010 to 43.3% [95% CI: 35.3%–51.3%] in 2019) and White adults (63.2% [95% CI: 56.7%–69.7%] in 2010 to 47.9% [95% CI: 42.4%–53.4%] in 2019) (Figure 2C, Supplementary Table S4). The prevalence of non-diabetes WI medications increased the least among non-Hispanic Black individuals (11.6% [95% CI: 5.7%–17.5%] in 2010 to 14.6% [95% CI: 7.9%–21.3%] in 2019) (Supplementary Table S6). The use of diabetes-specific WN medications was similar among all racial and ethnic groups (Supplementary Table S8).

Multivariate analysis of patterns of medication use

After adjusting for multiple covariates, over the period, there were significantly different odds of using WR, WI, or WN (diabetes-specific and non-diabetes) medications among adults with diabetes and overweight or obesity (Figure 3, all values in Supplementary Tables S10 or S13 and S14).

Adults with diabetes and overweight or obesity who were 75 years and older had lower odds of use of any WR medications (see Supplementary Tables S10) compared to 18- to 44-year-olds (adjusted odds ratio [aOR] 0.29 [95% CI: 0.18–0.47]). Similarly, Black and Hispanic (compared to White) adults (Black: aOR 0.38 [95% CI: 0.29–0.51]; Hispanic: aOR 0.49 [0.38–0.64]) and those with Medicaid or uninsured (compared to privately insured adults) (Medicaid: aOR 0.65 [95% CI: 0.47–0.90] and Uninsured: aOR 0.43 [95% CI: 0.25–0.75]) were less likely to use WR medications. Conversely, those with higher odds of use of WR medications included the following: those with BMI 35–39.9 (aOR 1.72 [95% CI: 1.27–2.33]) and BMI ≥40 (aOR 2.35 [95% CI: 1.76–3.14]), both compared to BMI 27–29.9, and those in the 2014–2016 period (aOR 1.96 [95% CI: 1.50–2.58]) and in the 2017–2019 period (aOR 3.11 [95% CI: 2.39–4.05]), both compared to those in the 2011–2013 period (Figure 3, values in Supplementary Table S10).

Adults with diabetes and overweight or obesity that had lower odds of using WI medications (Supplementary Table S10) were as follows: those with BMI 25–26.9 kg/m^2 (aOR 0.59 [95% CI: 0.34–1.01]) compared to those with BMI 27–29.9 kg/m^2 and those in the 2017–2019 period (aOR 0.73 [95% CI: 0.63–0.86]) compared to those in the 2011–2013 period. Adults with diabetes and overweight or obesity that had higher odds of use of WI medications included the following: 45- to 64-year-olds (aOR 1.25 [95% CI: 1.03–1.51]) compared to 18- to 44-year-olds; males (aOR 1.16 [95% CI: 1.00–1.33]) compared to females; those with BMI 35–39.9 kg/m^2 (aOR 1.29 [95% CI: 1.06–1.58]) compared to those with BMI 27–29.9 kg/m^2; and those with Medicaid and Medicare compared to those who were privately insured (Medicaid: aOR 1.73 [95% CI: 1.38–2.19]; Medicare: aOR 1.69 [95% CI: 1.36–2.08]).

For WN medications, adults with diabetes and overweight or obesity who had lower odds of use included the following: males (aOR 0.87 [95% CI: 0.76–0.99]) compared to females and Black and Hispanic compared to White adults (Black: aOR 0.65 [95% CI: 0.55–0.77]; Hispanic: aOR 0.79 [95% CI: 0.66–0.94]) (Figure 3; all values in Supplementary Table S10).

Continuity of weight-modifying medication use

Among adults with diabetes and overweight or obesity who used diabetes-specific WI (53.7%) medications during the first year, 92.7% (95% CI: 91.5%–93.8%) continued and 7.3% (95% CI: 6.2%–8.5%) discontinued their use in the second year, respectively (Figure 4, Supplementary Tables S11 and S12). Among adults with diabetes and overweight or obesity who used diabetes-specific WR (7.1%) medications during the first year, 83.6% (95% CI: 79.8%–87.5%) continued and 16.4% (95% CI: 12.5%–20.2%) discontinued their use in the second year, respectively. Among adults with diabetes and overweight or obesity who used diabetes-specific WN (62.4%) medications during the first year, 91.0% (95% CI: 89.9%–92%) continued and 9.0% (95% CI: 8.0%–10.1%) discontinued their use in the second year, respectively.

Among those who used non-diabetes WI medications (18.3%) during the first year, 84% (95% CI: 82.0%–86.0%) continued and 16.0% (95% CI: 14.0%–18.0%) discontinued use in the second year, respectively (Supplementary Tables S11, S12). Among adults with diabetes and overweight or obesity who used non-diabetes WR (4.4%)

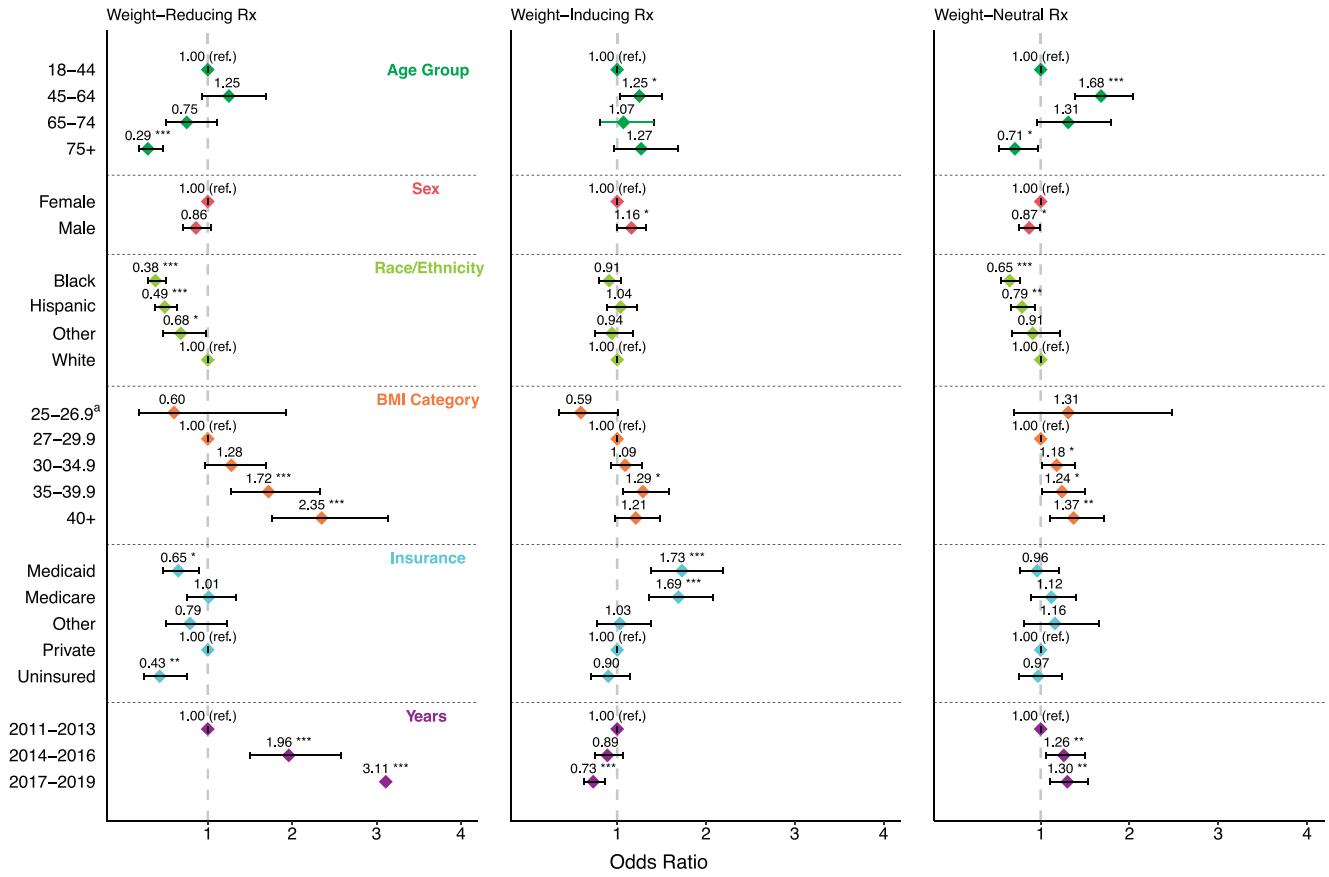

FIGURE 3 Odds ratios of use of weight-modifying medications among US adults with diabetes and overweight or obesity by age, sex, race and ethnicity, BMI category, insurance, and years: 2010–2019. Estimates were generated using Medical Expenditure Panel Survey (MEPS) Longitudinal Data and Prescription Medicines Data and adjusted for complex survey design to generate nationally representative estimates. Sample studied includes adults with overweight with diabetes who self-reported diabetes status in both years of the 2-year longitudinal panel. Weight-reducing medications include: GLP-1 agonists (dulaglutide, exenatide, liraglutide, and semaglutide), SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and combinations), appetite suppressants (naltrexone, phentermine, phentermine/topiramate combinations, and bupropion/naltrexone combinations), and neuroleptics/antiepileptics (topiramate, zonisamide, and ziprasidone). Weight-inducing medications include insulin, sulfonylureas/glinides (glyburide, glimepiride, glipizide, nateglinide, repaglinide), thiazolidinediones (pioglitazone), antiepileptics/neuroleptics (valproate, gabapentin, lithium, olanzapine, clozapine, and lithium), antidepressives (doxepin, nortriptyline, and mirtazapine), and glucocorticoids (methylprednisolone, prednisolone, hydrocortisone, and dexamethasone). [a]Overweight (25–26.9) category only includes Asian participants. Asian adults with diabetes are guideline-recommended to begin weight-reducing medications at a lower BMI (25.0) as compared to other populations. Year variable refers to the second year of which those surveyed participated. MEPS follows each individual for a 2-year period, and participants are enrolled in an overlapping panel design. We pooled panels together in three larger year categories for greater precision. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ [Color figure can be viewed at wileyonlinelibrary.com]

medications during the first year, 74.6% (95% CI: 68.6%–80.5%) continued and 25.4% (95% CI: 19.5%–31.4%) discontinued their use in the second year, respectively. Among adults with diabetes and overweight or obesity who used non-diabetes-specific WN (18.9%) medications during the first year, 89.2% (95% CI: 87.1%–91.3%) continued and 10.8% (95% CI: 8.7%–12.9%) discontinued their use in the second year, respectively (see Figure 4 and Supplementary Tables S11 and S12).

Sensitivity analyses

We estimated that 4.70% (unweighted $n = 520$) of all adults with diabetes (unweighted $n = 11{,}058$) had type 1 diabetes, consistent with prior reports [20]. In sensitivity analyses, we found no meaningful changes to study findings when adults with type 1 diabetes were excluded (Supplementary Figure S5). We also found no changes after limiting analyses to adults with prescriptions confirmed by pharmacy records (Supplementary Figure S6). Additionally, we examined multivariate analysis of medication use limited to only later years (2015–2019) to attenuate the effects of new medication approvals during the study period and found no major differences in direction and size of aORs by subgroup in later years as compared to the overall period (Supplementary Tables S10 and S13 and S14). Furthermore, we found no meaningful changes in the prevalence of certain conditions requiring treatment with specific therapies (e.g., non-diabetes WI, WN, or WR) over time in our cohort (Supplementary Tables S15/Figure S7).

FIGURE 4 Continuation or discontinuation of antiobesity medications among US adults with diabetes and overweight or obesity: 2010–2019. Estimates were generated using Medical Expenditure Panel Survey (MEPS) Longitudinal Data and Prescription Medicines Data and adjusted for complex survey design to generate nationally representative estimates. Sample studied includes adults with overweight with diabetes who self-reported diabetes status in both years of the 2-year longitudinal panel. We assessed prevalence of filling at least 1 medication prescription for each medication group in the first year and calculated the proportion who continued or stopped medication among first-year users. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

In this nationwide population-based serial cross-sectional study of use patterns of weight-modifying medications by adults with diabetes and overweight or obesity over the period 2010–2019, 64.9%, 13.5%, and 73.1% used any WI, WR, and WN medications, respectively. Over time, there was an increasing trend in the use of diabetes-specific WR and WN medications, as well as a decreasing trend in the use of diabetes-specific WI medications. Additionally, use of non-diabetes WR medications (anorexigenic) was remarkably low. In contrast, non-diabetes WI medications (orexigenic) were commonly used by 10% to 20% of adults with diabetes and overweight or obesity, and the number increased over the past decade. These findings underscore the importance of optimizing selection and continuity of diabetes and non-diabetes pharmacotherapy among adults with diabetes and overweight/obesity to support, not hinder, their weight loss.

Excess adiposity is foundational to the pathophysiology of T2D [21]. Our data demonstrate that, nationally, the therapeutic approach to diabetes management remains focused on reducing glycemic markers (i.e., hemoglobin A1c)—a manifestation of the disease and the underlying pathophysiology (excess adiposity) [21]. Indeed, several glucose-lowering drugs have long-term weight-gain effects, probably exacerbating the disease process [12]. Although our findings demonstrated a trend towards guideline-recommended management of overweight/obesity in adults with diabetes [5, 10, 11] (particularly since 2014–2019), people with diabetes and overweight/obesity were

4 to 20 times more likely to use diabetes-specific WI medications (48%–64%) than the preferred and guideline-recommended WR medications (3%–15%). We also noted that, when followed over 2 years, a larger cohort of adults with diabetes and overweight/obesity (up to twice as many) discontinued WR diabetes-specific medications compared to WN and WI medications. This calls for closer examination of the factors leading to poor initiation of and persistence with preferred WR drugs.

Compared to the long-term recognition of T2D as a chronic condition, it was not until 2013 that the American Medical Association recognized obesity as "a complex, chronic disease" [22]. Notably, despite these advances, the prevalence of obesity has progressively increased, and coverage for WR medications is still poor [22, 23].

Importantly, we found racial and ethnic disparities in weight management. There are several potential reasons for the inadequate use of WR medications by racial and ethnic minority patients. It is possible that clinicians are not prescribing these medications as a reflection of implicit bias or assumptions about weight management in minority populations [6, 24, 25]. Hence, there is still a need for more education among health care professionals in terms of recognizing obesity as a chronic relapsing disease [22, 26] and the benefits of long-term treatment [24, 25]. Alternatively, patients may not accept these medications because they cannot afford them or do not view obesity as a disorder that requires pharmacologic therapy. In addition, some medications required injection, which could be a limitation among either needle-phobic individuals or older adults with dexterity limitations. These trends could also be driven by high cost of medications [13, 14, 27] and/or lack of knowledge or familiarity with these medications by prescribers [24, 25]. For instance, the median average wholesale price for sulfonylureas (second generation) was reported to be 8 to 14 times lower than for exenatide, 10 to 18 times lower than for dulaglutide and semaglutide, and 12 to 22 times lower than for liraglutide [28].

After weight loss attempts with lifestyle intervention and/or pharmacotherapy, patients with excess adiposity often face a negative pathophysiological counter-response, limiting weight loss efforts [6, 29]. Hence, it was concerning to find patterns of increasing use of WI medications for other conditions than diabetes or excess weight at national levels, which will also counteract weight loss efforts. Prior studies have also raised awareness of increasing use of antidepressants, antiepileptics, and antipsychotic medications with WI effects in recent years [30, 31]. Our data confirm increasing trends of these medications being filled. In sensitivity analyses, we found that the prevalence of these conditions requiring treatment with specific WI therapies did not change substantially over time, indicating that prescribing of these obesogenic medications is not being driven by higher prevalence alone. Since most patients are treated for diabetes and obesity by their primary care clinicians, there may be an opportunity for education and quality improvement interventions such as electronic prompts and clinical decision support tools [13, 15]. It is also important to advocate for health insurance coverage for WR medications, to simplify prior authorization and extra requirements for eliminating the current roadblocks to evidence-based pharmacotherapy, to incentivize WR therapy as opposed to WI medications, and to consider quality measures that optimize weight-management strategies.

While lifestyle and dietary changes are the backbone of weight management, the efficacy of intensive lifestyle interventions in structured randomized controlled trials and real-world settings is limited to 3% to 8% of body weight, and this weight is often regained during follow-up [32–35]. This amount of weight loss is also not sufficient to effectively prevent or treat adiposity-related complications, which generally requires >10% to 15% of body weight loss [5, 11]. Indeed, several clinical practice guidelines recommend the addition of pharmacological interventions with approved medications for adults with BMI ≥ 27 kg/m^2 and >1 weight-related comorbidity (i.e., T2D) or for adults with BMI >30 kg/m^2 [5, 10, 11]. Moreover, the American Association of Clinical Endocrinologists and the Endocrine Society guidelines made these recommendations several years ago (e.g., 2012–2015) [5, 10]. However, their approval time was different, specifically for phentermine/topiramate in 2012, for naltrexone/bupropion in 2014, for liraglutide for diabetes in 2010 and for weight loss in 2014, and more recently for semaglutide (in doses approved for diabetes) in 2017. Recently, more potent agents such as tirzepatide or higher doses of semaglutide (approved for obesity treatment) have demonstrated even greater weight-loss effects (up to 15%–20% of body weight loss), including >30% of trial participants achieving up to ≥20% body weight loss compared to placebo—efficacy similar to that of some metabolic surgery procedures [29, 36–39].

This study has several limitations. MEPS data are based on household reports, which tend to underreport use, and may be subject to recall bias. However, prescriptions can be linked to pharmacy reports, which we examined in a sensitivity analysis; we found no differences in the patterns reported with those validated using pharmacy records. We also recognize that some of agents were approved early, whereas others were approved later during our study period. In sensitivity analyses, we found no differences in aORs of medication use in recent years compared to the whole period. In addition, MEPS does not permit us to precisely identify patients with long-standing T2D who are insulin-dependent and thus require insulin therapy. However, even such patients may benefit from addition of WR medications to mitigate insulin-associated weight gain and also lower insulin needs. Individuals with type 1 diabetes may require WI medications, specifically insulin, for survival. To address this nuance, we conducted a sensitivity analysis, and our findings did not change meaningfully when those with probable type 1 diabetes were excluded. It is certainly possible that some patients may use multiple medications with differential or similar effects on weight. However, considering all possible permutations of drug combinations would be technically prohibitive.

Strengths of our study include the ability to examine medication use patterns of the overall US population to a degree that is not possible using other databases. It also allows for unbiased estimates of disparities in medication use, which is essential as we work to address the racial, ethnic, and socioeconomic disparities in the burden of diabetes and overweight/obesity across the US. While it is true that our data predate the COVID-19 pandemic and the rapid

increase in attention to WR medications in 2022, our data offer a benchmark from which to compare future trends in the use of WI, WR, and WN medications. Another key innovation is that our data offer a glimpse into the continuity of use of WI, WR, and WN medications, an aspect not previously examined in cross-sectional analyses of medication use.

CONCLUSION

In this nationwide study of adults with diabetes and overweight/obesity, we found decreasing trends between 2010 and 2019 in the use of WI diabetes-specific and non-diabetes agents and increases in WR medications, although prevalence of use of WI medications remained higher than WR medications. Earlier adoption of WR medications was seen in some groups, and lagging adoption was seen among specific groups, especially ethnic minorities. Our findings suggest that diabetes management remains focused on reducing glycemic markers (i.e., hemoglobin A1c), a manifestation of the disease, and not targeting part of its underlying pathophysiology—excess adiposity [21]. These results represent a benchmark before the COVID-19 pandemic and may inform scientific societies, clinicians, advocacy groups, and policymakers to align prescribing with guidelines.O

AUTHOR CONTRIBUTIONS

Rodolfo J. Galindo developed the study's concept and, along with Mohammed K. Ali, Tegveer S. Uppal, Guillermo E. Umpierrez, and Rozalina G. McCoy, developed the initial study protocol. Tegveer S. Uppal performed the statistical analyses and database management. Rodolfo J. Galindo had full access to all the data analyses and takes responsibility for the integrity of the data and the accuracy of the results. All authors contributed to study concept, design, analysis of data, and interpretation of the data.

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CONFLICT OF INTEREST STATEMENT

Rodolfo J. Galindo received unrestricted research support (to Emory University) from Novo Nordisk, Dexcom, and Eli Lilly and consulting/advisory/honoraria fees from Sanofi, Eli Lilly, Novo Nordisk, Boehringer-Ingelheim, Bayer, Pfizer, Dexcom, Abbott, and Weight Watchers, outside the scope of this work. Rozalina G. McCoy has served as a consultant to Emmi on the development of patient education materials related to prediabetes and obesity and has received support (to Mayo Clinic) from UnitedHealthGroup, unrelated to this work. Guillermo E. Umpierrez has received unrestricted research support for research studies (to Emory University) from Merck, Novo Nordisk, Dexcom Inc, and Sanofi. Mohammed K. Ali has received research support (to Emory University) from Merck and consulting fees from Bayer and Eli Lilly, both outside the scope of this work. Tegveer S. Uppal received research support (to Emory University) from Merck, outside the scope of this work.

DATA AVAILABILITY STATEMENT

Deidentified patient data will be made available after 12 months of publication, upon reasonable request with an IRB-approved protocol to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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