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ORIGINAL ARTICLE

Real-world weight change among patients treated with glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitor and sulfonylureas for type 2 diabetes and the influence of medication adherence

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Summary

Aims

The study aims to examine real-world weight change and the role of medication adherence among patients with type 2 diabetes who initiated one of three drug classes: glucagon-like peptide-1 receptor agonist (GLP-1RA), dipeptidyl peptidase-4 inhibitor (DPP4) and sulfonylureas (SUs).

Materials and methods

A cohort of patients initiating one of the three drug classes was selected from a large US database of integrated electronic medical record and administrative claims. Adherence was defined as per cent of days covered ≥80% during the year following drug initiation. Weight change was calculated from drug initiation (−180, +30 d) to 1 year (±90 d) later. Multivariate regression controlled for baseline differences between adherent and poorly adherent patients and the addition of another drug class during follow-up.

Results

The study included 833 GLP-1RA, 2,272 DPP4 and 2,713 SU patients who contributed 2,279, 6,602 and 7,429 observations respectively. Patients initiating a GLP-1RA achieved the largest weight change (−2.46 kg of GLP-1RA, −1.26 kg of DPP4 and 0.18 kg of SU, $P < 0.01$). Adherent GLP-1 patients lost 1.73 kg more than poorly adherent patients, and adherent SU patients gained 1.11 kg more than poorly adherent patients (all $P < 0.01$). Adherent and poorly adherent DPP4 patients experienced approximately the same amount of weight loss.

Conclusions

Medication adherence can mediate observed weight loss in patients treated with a GLP1-RA or weight gain in those treated with an SU. Medication adherence was low in a real-world population, particularly for GLP-1RA, which displayed the strongest weight loss benefit. Because recent American Diabetes Association guidelines recommend selecting drug therapies that have a weight loss or weight neutral effect for the management of type 2 diabetes patients, patients should be encouraged to enhance their adherence to benefit the most from therapies that have weight loss properties.

Keywords: Medication adherence, real-world, type 2 diabetes, weight change.

Introduction

Weight management is a critical component of type 2 diabetes (T2D) management. Over 80% of patients with diabetes are overweight or obese, increasing their risk of cardiovascular disease (1). Benefits of weight loss in patients with T2D are well-documented in clinical trial settings. In the Look AHEAD and POWER trials, weight reduction in T2D patients achieved by behavioural intervention has been shown to reduce cardiovascular events, improve glycaemic control level and reduce the need for glucose-lowering medications (2–8). The 2017 American Diabetes Association guidelines recommend that providers consider the potential effect on weight when choosing glucose-lowering medications for overweight or obese patients (9). The guidelines indicate that many older glucose-lowering medications such as insulin, thiazolidinedione (TZDs) and sulfonylureas (SUs) may lead to weight gain. Among newer drug classes, dipeptidyl peptidase-4 inhibitors (DPP4s) have been shown to be weight neutral and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with weight loss (2,10–12).

Poor medication adherence can be a barrier to achieving clinical goals for patients with diabetes. Previous research has found that less than half of patients with T2D may be fully adherent to their diabetes medications, with estimated rates of medication adherence ranging between 34% and 47.3% for patients treated with a GLP-1, DPP4, SU or TZDs in the USA (13,14). Real-world evidence has shown that patients who are adherent to their diabetes medications have greater glycated haemoglobin (HbA1c) reductions after initiating the drug and lower medical care (nonpharmacy) costs, compared with poorly adherent patients (14,15).

The objective of this study is to describe real-world weight loss among patients treated with each of these drug classes and compare weight loss among patients who are adherent and poorly adherent to their diabetes medications. The hypothesis of this study is that adherence to these medications may moderate the effect of each class of medication on weight changes. Medication adherence is defined as the act of taking medications as prescribed by a physician, including the prescribed dose at the prescribed frequency. The measure of adherence employed in this study is based on administrative pharmacy claims that indicate whether a patient has the prescribed drug on hand (per cent of days covered [PDC]), a necessary condition for actually taking the medications, over an approximately 1-year follow-up period. This approach has been commonly used in the real-world medication adherence literature and is similar to quality metrics endorsed by the National Quality Forum. It has also been used in Medicare Star ratings, which measure adherence to oral antidiabetic agents as a group, rather than to a specific drug the patient has filled, which yield different estimates if the patient is taking multiple medications to treat diabetes (13,14,16,17).

Research design and methods

Data and patients

The Optum/Humedica SmartFile database (spanning January 2007 to December 2014) was used in this retrospective cohort study and is one of the largest integrated databases that include both administrative claims (used to measure medication adherence) and electronic medical records (used to measure weight change). Adult patients (aged 18 years and older) with T2D who initiated a GLP-1RA, DPP4 or SU were included in this study, and the initial date for each first prescription fill for the GLP-1RA, DPP4 or SU (index drug) was defined as the index date. Baseline was defined as the year prior to the index date, and follow-up was defined as the approximately 1-year period between the index date and a subsequent weight measurement. Study patients were required to have continuous health plan enrolment (1 year before and after the index date) and weight measurements at the index date and approximately 1 year later. Patients were excluded if they had a diagnosis of type 1 diabetes, secondary diabetes or gestational diabetes during the baseline or follow-up periods, defined based on International Classification of Diseases, Ninth Revision, Clinical Modification codes shown in Table S1. Patients initiating a GLP-1RA or DPP4 were selected based on National Drug Codes for each ingredient included in each class (GLP-1RA: exenatide and liraglutide; DPP4: sitagliptin, saxagliptin, linagliptin, and alogliptin; SU: chlorpropamide, glyburide, glipizide, and glimepiride). The database was compliant with the Health Information Portability and Accountability Act; all data were deidentified and thus exempt from institutional board review.

Study measures

Real-world study measures included change in weight, baseline patient characteristics and follow-up medication use. The outcome of this study was change in weight, which was measured from a visit near drug initiation (up to 180 d before or 30 d after drug initiation) to a second weight measurement 365 ± 90 d following drug initiation

(follow-up period). For patients with multiple weight measurements near drug initiation, the observation closest to the index date was selected. Patients with multiple observations of weight change approximately 1 year after medication initiation (365 d ± 90) contributed multiple estimates of change in weight.

Baseline characteristics included age, race/ethnicity, sex, body mass index (BMI; closest measure to index date up to 180 d before and 30 d after the index date), use of advanced T2D therapy (any prescription fill for diabetes medication other than metformin monotherapy during the baseline year, including other antidiabetic monotherapies or combinations) and presence of any diabetes complications during the baseline year. The presence of diabetes complications was assessed by using the Diabetes Complications Severity Index score, a 13-point scale scored from diagnostic, pharmacy and laboratory data, which has been shown to be associated with diabetes disease progression and greater risk of death.

In the main analysis, adherence to the index drug was measured by using a single variable based on PDC with a nonoverlapping supply of the index drug (GLP-1RA, DPP4 or SU) during the follow-up period. Consistent with prior literature and quality measures, patients were classified as adherent if PDC was $\geq$ 80% (14,17,18). In a subanalysis, patients were further divided into four groups: PDC $\geq$ 90% (very adherent), PDC between 80% and 90%, PDC between 50% and 80% and PDC $<$ 50% (very poorly adherent) and weight outcomes for very adherent patients were compared with those for very poorly adherent patients.

Other measures of the patient's regimen of diabetes drugs during follow-up were examined including discontinuation of the index drug, ending dosage of the index drug and changes to a regimen of diabetes drugs other than the index drug. Discontinuation of the index drug was defined as at least a 30-day gap in medications on hand with no subsequent fills through the end of the follow-up period. The full dose for each drug components is defined based on prescribing information for each drug in patients with no need for dosage adjustment (exenatide: $\geq$20 μg of BID or 2 mg of QW, liraglutide: $\geq$1.2 mg, sitagliptin: $\geq$100 mg, saxagliptin: $\geq$5 mg, linagliptin: $\geq$5 mg, alogliptin: $\geq$25 mg, chlorpropamide: $\geq$250 mg, glyburide: $\geq$2.5 mg, glipizide: $\geq$5 mg and glimepiride: $\geq$1 mg). Changes in the regimen of diabetes drug (other than the index drug) may include addition and discontinuation of other (nonindex) T2D drugs during follow-up, which was measured by comparing drugs on hand during the 90-day period before the first (index) and second weight measurements.

Analysis

The analysis compared changes in weight across patients taking each of the three index drugs (GLP-1RA, DPP4 and SUs) and also compared weight change among adherent and poorly adherent (or very adherent and very poorly adherent) patients in each drug class. A subgroup analysis was conducted to describe how weight change varies by baseline BMI level.

To control for differences in patient characteristics that may confound the relationship between weight change and adherence, multivariate models of weight change were estimated for each drug class. The multivariate model controlled for baseline factors (BMI, age, any diabetes complications and use of advanced diabetes therapies) and follow-up measures of diabetes medication use (adherence to the index drug and the addition of other [nonindex] T2D medications). Analyses were weighted such that each patient contributed equally to the results (weight equal to the inverse of the number of weight measurements for a patient) and standard errors were corrected for multiple observations per patient by using clustered standard errors. Sensitivity analyses were conducted to examine (i) the influence of race/ethnicity and sex, which were excluded from the main specification because these factors are correlated with adherence, and (ii) the impact of including baseline HbA1c level. The model was estimated by using ordinary least squares and, as a linear model, each coefficient demonstrates how much weight increased or decreased with every 1 point increase in the value of the covariate.

The statistical software STATA® (StataCorp) was used for the regression analysis, and EXCEL® (Microsoft) was used for all other analyses. Chi-square tests were used for comparisons of categorical variables. Two-sided *t*-tests were used for comparisons of continuous variables. A value of $P < 0.01$ was used to determine significance.

Results

Patients

A total of 5,818 patients who initiated either GLP-1RA (833), DPP4 (2,272) or SU (2,713) contributed a total of 16,310 observations in the study (2,279 GLP-1RA, 6,602 DPP4 and 7,429 SU; Table 1). Among patients who initiated GLP-1RA therapies, 53% were treated with liraglutide and the remaining patients initiated exenatide. Among patients who initiated DPP4 therapies, most (73%) initiated sitagliptin, followed by saxagliptin (21%) with the remainder treated with linagliptin or alogliptin. Among patients who initiated SU therapies, 45% initiated

Table 1 Patient baseline characteristics and medication use during follow-up

	GLP-1RA	DPP4	SU
Number of patients	833	2,272	2,713
Number of weight measurements per patient, mean (SD)	2.74 (2.20)	2.91 (3.02)	2.74 (2.52)
Baseline patient characteristics			
Age, mean (SD)	56 (10)	62 (12)	63 (14)
Age, % (*N*)			
Under 45	14 (116)	9 (205)	9 (232)
45–64	63 (526)	46 (1,054)	43 (1,165)
65 and older	23 (191)	45 (1,013)	49 (1,316)
Sex, % male (*N*)	47 (392)	54 (1,236)	55 (1,495)
Race, % white (*N*)	83 (693)	79 (1,799)	80 (2,167)
Weight, kg, mean (SD)	110 (24)	97 (25)	97 (24)
BMI, kg/m^2, mean (SD)	38 (8)	34 (8)	34 (7)
Patients with nonmissing BMI, % (*N*)[a]	97 (810)	97 (2,198)	96 (2,594)
BMI, kg/m^2, % (*N*)			
< 25	1 (12)	8 (186)	9 (234)
25.0–29.9	10 (79)	26 (571)	25 (657)
30.0–34.9	26 (212)	28 (624)	29 (752)
35.0–39.9	27 (221)	20 (443)	19 (495)
≥ 40.0	35 (286)	17 (374)	18 (456)
HbA1c (%), mean (SD)	8.2 (3)	8.0 (2)	8.0 (3)
HbA1c $\leq 7\%$, % (*N*)	65.2 (543)	65.7 (1,463)	62.8 (1,704)
Any diabetes complications[b], % (*N*)	61 (511)	67 (1,530)	66 (1,791)
Baseline medications			
No T2D medications	9 (75)	15 (357)	31 (837)
Metformin monotherapy only	15 (125)	24 (536)	41 (1,111)
Use of advanced T2D medications[c], % (*N*)	76 (633)	61 (1,379)	28 (765)
Medication use during follow-up			
Index drug			
PDC (index drug), mean (SD)	51 (0.3)	59 (0.3)	62 (0.3)
Adherent to index drug (PDC $\geq 80\%$), % (*N*)	24 (203)	35 (784)	40 (1,094)
Very adherent (PDC $\geq 90\%$), % (*N*)	8 (66)	15 (337)	20 (552)
Very poorly adherent (PDC $< 50\%$), % (*N*)	47 (394)	37 (848)	34 (911)
Discontinued, % (*N*)	50 (416)	41 (930)	38 (1,020)
Other (nonindex) diabetes drugs			
Addition of other T2D drug(s) after GLP-1RA/DPP4 initiation, % (*N*)	3.5 (29)	3.7 (83)	2.0 (53)
PDC with metformin, mean (SD)	47 (0.4)	48 (0.4)	42 (0.4)

Statistical significance: All differences in baseline patient characteristics between GLP-1RA and DPP4s and GLP-1RA and SU patients were statistically significant, except race and HbA1c (mean and per cent $< 7\%$). All baseline differences between DPP4-treated and SU-treated patients were not significant. All differences in baseline medications and adherence to the index drug were statistically significant. Differences in the addition of other T2D medications were statistically significant except for between GLP-1RA and DPP4 medications. Differences in PDC by metformin were significant between SU and the other two drugs but not between GLP-1RA and DPP4.

[a]Patients were missing baseline BMI if no height measurements are available for that patient; all patients in the study were required to have a baseline weight measurement.

[b]Patients were considered to have diabetes complications if their Diabetes Complications Severity Index (DCSI) score was ≥ 1[15] and included the following seven categories of complications: cardiovascular disease, nephropathy, retinopathy, peripheral vascular disease, stroke, neuropathy and metabolic.

[c]Patients were considered to have used advanced drugs for T2D if they were not drug naïve and used any drugs other than metformin monotherapy.

Abbreviations: BMI, body mass index; DPP4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; *N*, number; PDC, per cent of days covered; SD, standard deviation; SU, sulfonylurea; T2D, type 2 diabetes.

glipizide followed by glimepiride (34%) and glyburide (20%), and one patient was treated with chlorpropamide. Between 75% and 100% of patients were treated with at least the full dose, except glimepiride-treated patients; about half of whom were treated with the full dose by their last fill in the follow-up period.

Compared with patients initiating either DPP4 or SU, GLP-1RA patients were younger, more likely to be female

and white (all $P < 0.05$, Table 1). Baseline weight and BMI were highest among GLP-1RA patients compared with DPP4 and SU patients. The proportion of patients with any diabetes complications among GLP-1RA patients was lower than the DPP4 and SU patients. Compared with patients initiating a GLP-1RA or DPP4, patients initiating an SU were less likely to be treated with other antidiabetic drugs (other than metformin monotherapy), suggesting that their treatment is earlier in the progression of T2D or, possibly, they had poorer access to appropriate medical care ($P < 0.01$).

Adherence was lower among GLP-1RA-treated patients compared with those treated with a DPP4 or SU (Table 1). About one-quarter of the GLP-1RA-treated patients were adherent, compared with 35% and 40% of DPP4 and SU-treated patients respectively. A similar pattern across drug classes was observed among patients who were very adherent (PDC $\geq$ 90%).

Change in weight

Patients who were treated with a GLP-1RA lost more weight (−2.46 kg) than patients treated with a DPP4 (−1.26 kg) or with an SU (0.18 kg; Table 2, not regression adjusted). The impact of adherence on weight change varied by drug class; adherent GLP-1RA-treated patients lost more weight (−4.30 kg) compared with poorly adherent patients (−1.88 kg, $P < 0.01$). However, weight loss was the same among adherent and poorly adherent DPP4-treated patients. Both groups of patients lost just over 1 kg ($P < 0.01$). Adherent SU-treated patients gained under 1 kg (0.78 kg), and poorly adherent patients lost a small amount of weight (−0.22 kg); both weight changes are statistically significant from zero. A similar pattern was found when very adherent and very poorly adherent patients were compared. Very adherent patients treated with a GLP-1RA lost the most weight (−5.14 kg), while very poorly adherent GLP-1RA-treated patients lost the least (−1.61 kg; $P < 0.01$).

Regression-adjusted results were similar and slightly attenuated after adjustment to control for differences between adherent and poorly adherent patients within each drug class (Figures 1 and 2 and Table S2). Adherent GLP-1RA-treated patients lost 1.73 kg more than poorly adherent patients ($P < 0.01$), while weight loss was similar for adherent and poorly adherent DPP4-treated patients. Adherent patients treated with an SU gained weight, resulting in a 1.11-kg increase in weight among adherent patients relative to poorly adherent patients (Figure 1). Similarly, very adherent GLP-1 patients lost 2.58 kg more than very poorly adherent patients and very adherent SU patients gained 1.71 kg more than very poorly adherent patients (all $P < 0.01$). Very adherent and very poorly adherent DPP4 patients experienced approximately the same amount of weight loss (Figure 2).

The regression analysis found that older patients (age $\geq$ 65) lost more weight (1–2 kg) than younger patients (age $<$ 45); this was statistically significant for DPP4-treated and SU-treated patients, but not for GLP1-RA-treated patients. The number of patients under age 45 treated with GLP-1RA was much lower, a likely reason for the lack of statistical significance. Patients with larger BMI at baseline lost more weight. Sensitivity analysis around the inclusion of other factors in the model, including sex, race/ethnicity and baseline HbA1c, did not alter conclusions regarding the association between medication adherence and weight change across drug cohorts.

Table 2 Change in weight (not regression adjusted) and medication adherence approximately 1 year after drug initiation

	GLP-1RA (*N* = 833)	DPP4 (*N* = 2,272)	SU (*N* = 2,713)	*P*-value (DPP4 vs. GLP-1RA)	*P*-value (SU vs. GLP-1RA)	*P*-value (DPP4 vs. SU)
Change in weight approximately 1 year after drug initiation, (kg), mean (SE)						
Overall	−2.46 (0.19)	−1.26 (0.08)	0.18 (0.08)	<0.01	<0.01	<0.01
Adherent (PDC ≥ 80%)	−4.30 (0.32)	−1.21 (0.13)	0.78 (0.11)	<0.01	<0.01	<0.01
Poorly adherent (PDC < 80%)	−1.88 (0.22)	−1.29 (0.10)	−0.22 (0.10)	0.01	<0.01	<0.01
Difference: adherent minus poorly adherent, mean [*P*-value]	−2.42 [<0.01]	0.08 [0.62]	1.00 [<0.01]			
Very adherent (PDC ≥ 90%)	−5.14 (0.46)	−1.03 (0.17)	0.77 (0.16)	0.01	<0.01	<0.01
Very poorly adherent (PDC < 50%)	−1.61 (0.20)	−1.32 (0.14)	−0.72 (0.14)	0.23	<0.01	<0.01
Difference: very adherent minus very poorly adherent, mean [*P*-value]	−3.53 [<0.01]	0.29 [0.19]	1.49 [<0.01]			

Abbreviations: DPP4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; *N*, number; PDC, per cent of days covered; SE, standard error; SU, sulfonylurea.

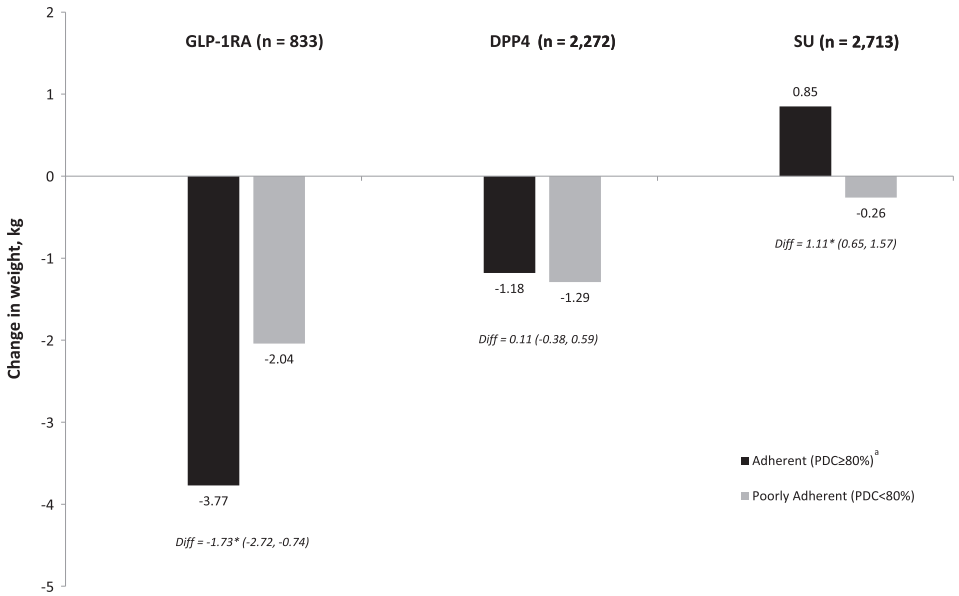

Figure 1 Regression-adjusted weight change after drug initiation in adherent and poorly adherent patients, by T2D drug class. 833 GLP-1RA, 2,272 DPP4 and 2,713 SU patients contributed a total of 16,310 observations in the study (2,279 GLP-1RA, 6,602 DPP4 and 7,429 SU). Results are regression-adjusted to control for differences in baseline patient characteristics and the addition of other diabetes drugs during follow-up. To account for multiple observations per patient, results were weighted such that each patient contributes equally (weight equals to the inverse of the number of weight measurements). Standard errors were clustered at the patient level. *Statistically significant at 99% confidence levels. [a]Adherence is defined as PDC $\geq$ 80%; poor adherence is defined as PDC $<$ 80%. PDC is the percentage of days covered by supply of a GLP-1RA, DPP4 or SU between the index date and the second weight measurement date. Abbreviations: DPP4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; PDC, per cent of days covered; SU, sulfonylurea; T2D, type 2 diabetes.

The subgroup analysis (Table 3) showed that a higher baseline BMI was associated with a statistically significant greater weight loss across all drug classes. Adherent and poorly adherent patients in the highest BMI category (BMI $\geq$ 40 kg/m^2) lost weight after starting the drug, even among poorly adherent patients across all categories. Consistent with the main results, weight loss in this highest BMI category was not associated with adherence among DPP4-treated patients, adherent GLP-1RA-treated patients lost more weight than poorly adherent patients, and adherent SU-treated patients either gained weight or lost less weight than poorly adherent SU-treated patients.

Discussion

Consistent with evidence from clinical trials, this study demonstrated that GLP-1RA treatment is associated with weight loss, SU treatment is associated with weight gain, and DPP4 treatment is weight neutral in real-world patients (11,12). Additionally, adherence to GLP-1RA treatment appears to enhance its weight loss effect and adherence to SU appears to amplify weight gain. In contrast, patients treated with DPP4 experienced small weight changes and adherence to DPP4 treatment had no effect on weight.

To our knowledge, several observational studies have quantified the weight change in real-world T2D patients. A prior real-world study of patients treated with liraglutide also found weight loss effect similar to this study. The results suggest that patients with higher baseline BMI lost the most weight (patients with baseline BMI $\geq$ 40 kg/m^2 lost about 4 kg), which are similar to patients in our study with a similar baseline BMI (19). Another study that focuses on the association between adherence and weight change found that T2D patients with higher levels of medication adherence experienced the most weight loss. Surprisingly, this was observed regardless of whether the patient's diabetes medications were associated with weight gain or weight loss. The authors concluded that weight loss likely leads to greater medication adherence (20). In contrast, the present study found weight loss among adherent patients only if the drug was associated with weight loss. Furthermore, weight loss (or gain) in this study was magnified among patients who were very adherent to drugs associated with weight loss (or gain). It is likely that this study found different results because of the use of a more precise measure of medication adherence (based on prescription

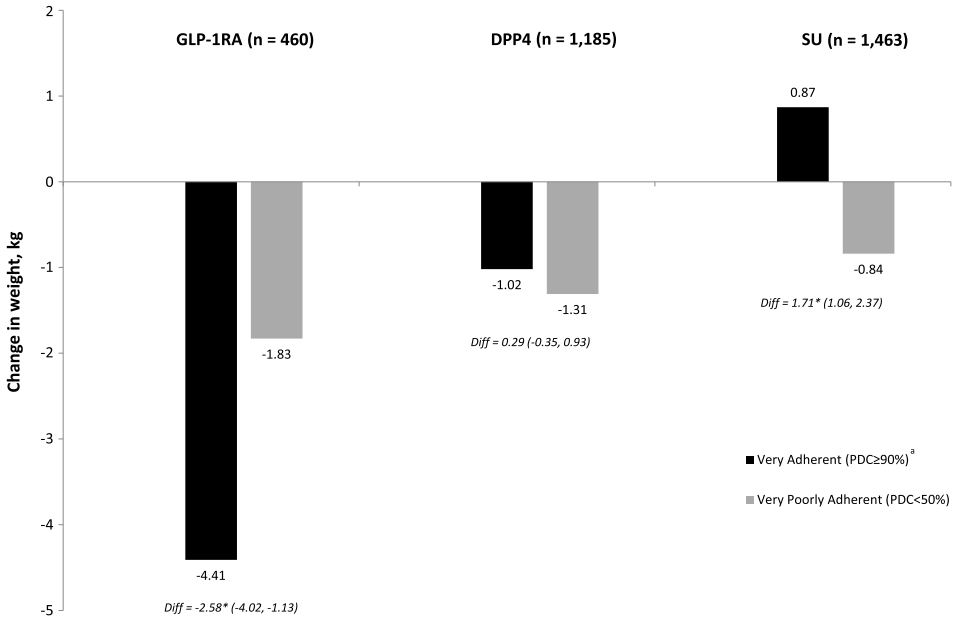

Figure 2 Regression-adjusted weight change after drug initiation in very adherent and very poorly adherent patients, by T2D drug class. 460 GLP-1RA, 1,185 DPP4 and 1,463 SU patients contributed a total of 8,352 observations in the study (1,276 GLP-1RA, 3,265 DPP4 and 3,811 SU). Results are regression-adjusted to control for differences in baseline patient characteristics and the addition of other diabetes drugs during follow-up. To account for multiple observations per patient, results were weighted such that each patient contributes equally (weight equals to the inverse of the number of weight measurements). Standard errors were clustered at the patient level. *Statistically significant at 99% confidence levels. [a]Very adherent is defined as PDC $\geq$ 90%; very poorly adherent is defined as PDC $<$ 50%. PDC is the percentage of days covered by a nonoverlapping supply of the GLP-1RA, DP4 or SU between the index date and the second weight measurement date. Abbreviations: DPP4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; PDC, per cent of days covered; SU, sulfonylurea; T2D, type 2 diabetes.

drug claims rather than a four-question patient survey). This study follows patients initiating a particular drug and thus more precisely classifies patients. The prior study classified patients into two groups: patients taking any weight-increasing medication (TZD, SU or insulin) compared with everyone else, with DPP4-treated patients excluded from the analysis. Furthermore, this study may more closely identify the relationship between weight change and adherence because patients are followed after initiation of the drug. This study was not designed to identify the causal relationship, but two hypotheses are consistent with the observations. Initiation of a drug and adherence to that drug may influence changes in weight, although patients may be heterogeneous in how the drug affects their weight and how they may then respond regarding their ongoing use of that medication. Patients who do not lose weight while taking a GLP-1, for example, may become discouraged and choose to stop taking it or cut back. However, findings of this study are inconsistent with the idea that patients who gain weight while taking SUs may cut back on their drugs; the results suggest that more adherent patients treated with an SU gain more weight.

The findings of this study should be considered in light of several limitations. First, this study was observational in nature and relied on data from administrative claims and electronic medical records and thus is subject to limitations inherent in these types of data. Medication adherence is based on prescription drug fills. Because a patient may not actually take all doses of a filled prescription, medication adherence is likely to be overstated, which would bias the study findings related to adherence towards zero. Additionally, several potentially confounding differences between adherent and poorly adherent patients could influence weight outcomes. Some of these factors (age, baseline BMI, baseline T2D medications and presence of diabetes complications) were controlled for using multivariate regression. However, other unobserved factors such as lifestyle interventions (including diet and exercise) and patient–provider interactions (such as advice patients received from the managing physician) that may also affect weight outcomes were not possible to observe and control for in this study.

Second, adherence was measured over a relative short period of approximately 1 year after the initiation of the

Table 3 Subgroup analysis: change in weight (not regression adjusted) and medication adherence approximately 1 year after drug initiation, by BMI

	GLP-1RA (*N* = 833)	DPP4 (*N* = 2,272)	SU (*N* = 2,713)
Number of patients with nonmissing BMI (%)[a]	810 (97)	2,198 (97)	2,594 (96)
Overweight and obese patients (BMI ≥ 25kg/m^2)			
Number of patients	798	2,012	2,360
Adherent (PDC ≥ 80%), % (*N*)	25 (196)	35 (695)	41 (958)
Baseline BMI (kg/m^2), mean (SE)	38 (0.25)	35 (0.15)	35 (0.14)
Change in weight approximately 1 year after drug initiation, (kg), mean (SE)			
Overall	−2.80 (0.15)	−1.40 (0.08)	0.01 (0.08)
Adherent (PDC ≥ 80%)	−4.38 (0.33)	−1.34 (0.14)	0.54 (0.12)
Poorly adherent (PDC < 80%)	−2.32 (0.17)	−1.43 (0.10)	−0.34 (0.11)
Difference: adherent minus poorly adherent, mean [*P*-value]	−2.06 [<0.01]	0.09 [0.58]	0.88 [<0.01]
BMI ≥ 40			
Number of patients	286	374	456
Adherent (PDC ≥ 80%), % (*N*)	30 (86)	31 (117)	34 (156)
Baseline BMI (kg/m^2), mean (SE)	46 (0.31)	46 (0.29)	46 (0.26)
Change in weight approximately 1 year after drug initiation, (kg), mean (SE)			
Overall	−4.96 (0.31)	−3.27 (0.29)	−1.55 (0.25)
Adherent (PDC ≥ 80%)	−5.91 (0.57)	−3.65 (0.50)	−0.63 (0.38)
Poorly adherent (PDC < 80%)	−4.59 (0.37)	−3.10 (0.35)	−2.03 (0.33)
Difference: adherent minus poorly adherent, mean [*P*-value]	−1.32 [0.05]	−0.55 [0.37]	1.40 [<0.01]
BMI < 40			
Number of patients	524	1,824	2,138
Adherent (PDC ≥ 80%), % (*N*)	22 (114)	36 (648)	41 (886)
Baseline BMI (kg/m^2), mean (SE)	34 (0.18)	31 (0.11)	31 (0.10)
Change in weight approximately one year after drug initiation, (kg), mean (SE)			
Overall	−1.20 (0.23)	−0.81 (0.08)	0.56 (0.08)
Adherent (PDC ≥ 80%)	−3.14 (0.37)	−0.78 (0.12)	1.05 (0.12)
Poorly adherent (PDC < 80%)	−0.66 (0.27)	−0.82 (0.10)	0.22 (0.10)
Difference: adherent minus poorly adherent, mean [*P*-value]	−2.48 [<0.01]	0.04 [0.80]	0.83 [<0.01]

[a]Patients were missing baseline BMI if no height measurements are available for that patient; all patients in the study were required to have a baseline weight measurement.

Abbreviations: BMI, body mass index; DPP4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; *N*, number; PDC, per cent of days covered; SE, standard error; SU, sulfonylurea.

index drug. Thus, whether there is a sustained association between adherence and weight loss/gain is unknown. The results may not be generalized to longer periods of time or larger weight loss/gain effect.

Third, medication adherence is also known to be associated with glycaemic control level, which may be associated with change in body weight (21,22). It is important to understand the mechanisms among adherence, treatment-emerged weight changes and glycaemic control in patients treated by different drug classes. While the present study collects information on patient's baseline HbA1c, information about how patients' glycaemic control level changed at the end of the follow-up period was not collected. Future research analysing the association among adherence, weight change and glycaemic control would be useful in understanding the role of adherence in diabetes outcomes. In conclusion, this was the first real-world study to examine changes in weight among patients treated with DPP4 and SU; it also added to the limited body of evidence on real-world weight loss among GLP-1RA-treated patients. This study was not designed to compare the impact of medication adherence on weight changes across drug classes, as patients taking each class of medication differ in important ways. Further, clinical trials have documented how treatment with these medications may differentially impact weight (23,24). Greater adherence to GLP-1RA treatment resulted in a greater level of weight loss. Adherence to DPP4 did not have a significant association with weight change, whereas adherence to SU was significantly associated with weight gain. Taken together with the latest American Diabetes Association guidelines that recommend selecting drug therapy that has weight loss or weight neutral effect for the management of overweight/obese T2D patients, the present study adds to a body of literature highlighting the importance of adherence in the management of patients with T2D. The findings that medication adherence can mediate

observed weight loss in patients treated with a GLP1-RA or weight gain in those treated with an SU may have important implications for clinical practice. If adherence may reinforce or counteract weight loss efforts by the patient, depending on the class of medications, patients may benefit the most from being adherent to therapies that have weight loss properties.

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Author contributions

All authors were involved in the conception and design of the study, critical review of the results and manuscript and final approval of the published version. ET, GC, RT and JZ conducted the data collection and analyses; GC and JZ drafted the manuscript.

Disclosures

John Yee is an employee of Intarcia Therapeutics and owns stock options. Ginger Carls, Edward Tuttle, Ruo-Ding Tan and Jason Zhu are employees of Analysis Group, Inc., which has received consultancy fees from Intarcia Therapeutics. Steven Edelman and William Polonsky are on the Intarcia Advisory board and have not received any compensation for any work relating to this manuscript.

Previous presentation

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1: Diagnosis codes
Table S2: Estimated coefficients from the multivariate linear regression model of change in weight approximately one year after initiation