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Correlates of second-line type 2 diabetes medication selection in the USA

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ABSTRACT

Objective Past research provides insufficient evidence to inform second-line diabetes medication prescribing when metformin is no longer sufficient. We evaluated patient, prescriber, and health plan characteristics associated with selection of second-line diabetes medications in the USA.

Research design and methods We used a multiple case-comparison study design to identify characteristics associated with the probability of starting each of six second-line diabetes medication alternatives within 77 744 adults enrolled in commercial or Medicare Advantage health plans from 2011 to 2015. National administrative data were provided by a large commercial health payer. Multinomial logistic regression models were used to identify characteristics independently associated with selecting each diabetes drug class.

Results From 2011 to 2015, sulfonylureas still represented 47% of all second-line drug starts, with proportionately higher use in patients ≥75 years of age (63% of drug starts). Basal insulin was more likely to be selected when a past A1c test result was >10% (13.0% vs 4.5% for those with A1c <8%; p<0.001). Initiation of a glucagon-like peptide-1 receptor agonist was associated with being female (10.1% vs 6.0% for male; p<0.001) and having a diagnosis code for obesity (10.8% vs 6.9% for no diagnosis; p<0.001). For all drug classes, the recent prescribing behavior of the provider was a strong correlate of subsequent second-line drug selection.

Conclusions Sulfonylureas continue to represent almost half of second-line diabetes medication starts in the USA. This could reflect overuse for some groups such as older adults, for whom some alternatives may be safer, although more costly and potentially less effective. Future research should compare outcomes of medication choices and conditions under which particular classes are most effective.

Significance of this study

What is already known about this subject?

- Past research provides insufficient evidence to inform second-line diabetes medication prescribing when metformin is no longer effective.

What are the new findings?

- This study found that sulfonylureas remain the most commonly prescribed second-line diabetes drug class, despite the emergence of newer classes that do not cause weight gain or hypoglycemia.
- This pattern may reflect overuse of sulfonylureas for certain patient groups such as older adults, for whom some alternatives may be safer, although more costly.

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

- In general, provider characteristics and recent prescribing patterns showed strong associations with diabetes drug class selection, suggesting a need for further research on whether and how provider behavior can be influenced to promote evidence-based medication prescribing.

INTRODUCTION

Over the past two decades, there has been a sharp increase in the number of therapeutic drug classes to treat type 2 diabetes (T2D).[1] Although metformin has remained a cornerstone of initial T2D management, most patients eventually require the addition of a second or third agent to achieve goals for glucose control.[1 2] Unfortunately, there is insufficient past research to guide the optimal choice of second-line medication when metformin is no longer sufficient.[3]

Current guidelines allow for shared clinical decision-making based on goals for glucose and body weight outcomes, avoidance of possible side effects such as hypoglycemia, drug costs, and patient preference.[1 2] Such guidance is likely to yield high variation in treatment selection, which may be driven more by drug cost or a physician's past experience, rather than evidence for superior effectiveness. Little is currently known about the key determinants of diabetes medication prescribing in real-world practice.

This study was designed to evaluate the characteristics of patients, providers, and health plans that are associated with selection of the most common six classes of second-line T2D medications. Understanding treatment patterns and correlates of T2D medication selection is important because it can help identify possible reasons for overuse or underuse of particular medications. Moreover, this study will inform future research

Table 1 Trade-offs among existing diabetes drug treatment alternatives

	DPP4	GLP1	INS/B	SGLT2	SFU	TZD
First on market	2006	2005	NPH (isophane insulin)1982; Lantus 2000	March 2013	1950s	1997
Route	Oral	Injection	Injection	Oral	Oral	Oral
Mean A1c-lowering*	0.25%–1.0%	0.8%–1.5%	No limit	0.5%–1.0%	1.0%–1.5%	0.5%–1.5%
Hypoglycemia	No	No	Yes	No	Yes	No
Cost†	$428–$436	$527–$831	$165–$355	$470	$50–$94	$349–$355
Body weight	Neutral/loss	Loss	Gain	Loss	Gain	Gain
Other cautions	Kidney disease; ketoacidosis; pancreatitis	Pancreatitis; thyroid cancer; gastrointestinal upset		Urine and vaginal infection; kidney disease; fractures; caution elderly ketoacidosis	Caution elderly	congestive heart failure; liver disease; edema; fractures

*Range of mean A1c reductions from synthesis of multiple trials.[9]
†Range of median wholesale prices for monthly supply.[10]
DPP4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptide-1 receptor agonists; INS/B, long-acting or intermediate-acting insulin given as a basal (rather than mealtime) injection; SGLT2, sodium-glucose cotransporter 2 inhibitors; SFU, sulfonylurea or meglitinides; TZD, thiazolidinediones.

that evaluates the comparative effectiveness of different diabetes treatment options on glycemic control, diabetes complications, potential adverse treatment outcomes, and direct medical expenditures.

RESEARCH DESIGN AND METHODS

Study design and exposures of interest

Using administrative databases including more than 53 million health plan enrollees, we applied a multiple case-comparison study design to evaluate correlates of a first fill for one of six second-line T2D medication classes received by patients who previously were prescribed metformin alone. The six diabetes drug classes compared were dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP1) receptor agonists, long-acting or intermediate-acting insulin given as a basal (rather than mealtime) injection (INS/B), sodium-glucose cotransporter 2 (SGLT2) inhibitors, sulfonylurea or meglitinides (SFU), and thiazolidinediones (TZD). An overview of these medications is displayed in table 1. Because this research used coded, non-identifiable data, the Northwestern University Institutional Review Board judged that this work was not classifiable as human subjects research.

Study population

The study included health plan enrollees nationally who were ≥18 years of age and had diabetes treated with metformin alone before recording a first fill for a second-line diabetes medication. Individuals who met the following three criteria were considered to have T2D: (1) ≥1 pharmacy claim for one of the six diabetes medication classes of interest (we refer to the first dispensing date as the 'index date'); (2) ≥1 inpatient or outpatient medical claim with a diabetes diagnosis code occurring on or before the index date; and (3) ≥1 pharmacy claim for metformin in the 180 days before the index date. We excluded patients who did not also have evidence of metformin pharmacy claims in the 180 days *after* the index date. In addition, we excluded patients with a fill for any other T2D medication before the index date. Finally, we excluded patients with evidence of a pregnancy or a condition or treatment that might cause secondary diabetes, including hemochromatosis, acromegaly, cystic fibrosis, or more than 21 days of an oral corticosteroid medication within 180 days of the index date. Details regarding the definitions for these criteria are available in the online supplementary appendix.

Measures and outcomes

The primary study outcome was the probability of a first prescription fill for a drug in each of the six T2D medication classes. We explored associations with independent variables believed to be related to the likelihood of prescribing a particular drug class. Patient-level characteristics included gender, age, race/ethnicity, Charlson Comorbidity Score,[4] and presence/absence of a diagnosis code for obesity; most recent hemoglobin A1c test result (categorized as <8%, 8%–9.9%, ≥10%, or 'no value available'); census region of the individual's home zip code; and indicators of utilization within 90 days of the index date that might influence medication choice (eg, presence/absence of a diagnosis of hypoglycemia; presence/absence of a hospitalization; presence/absence of a diagnosis of poorly controlled diabetes; total patient out-of-pocket expenditure). Provider-level or 'prescriber'-level variables included specialty type (family physician, general internist, endocrinologist,

nurse practitioner, or 'other'); a prescribing index reflecting the percentage of a provider's patients who have diabetes; and indicators for high versus low probability of recent prescribing of each of the six drug classes (based on the percent of a provider's total T2D medication prescriptions that were for DPP4s, GLP1s, INS/Bs, SFUs, SGLT2s, or TZDs). Health plan-level variables included an index of the 'richness' of health coverage (ie, the median value of the percentage of total healthcare costs paid by the patient, for all persons in the same health plan); an indicator variable for enrollment in a Medicare versus commercial health plan; and the type of plan design (health maintenance organization (HMO); preferred provider organization (PPO); point of service (POS); indemnity (ie, traditional fee for service); exclusive provider organization; or other plan type). Please see the online supplementary appendix for additional details.

Data sources

Data sources included health plan enrollment files, medical inpatient and ambulatory claims, and pharmacy claims. Although most patients had recent laboratory claims for A1c tests, test results are typically not available from administrative data. However, the laboratory claims file did include results for 36% of A1c claims. The availability of these results was comparable across the six T2D medication classes. Information about race and ethnicity also was not consistently available in these administrative data but was imputed by the data vendor using a mix of individual-level and neighborhood-level characteristics.

Statistical analysis

Descriptive statistics for baseline patient, provider, and plan characteristics were summarized across each of the six drug classes. Student's t-tests were used to compare continuous variables; X^2tests were used to compare categorical variables. Multinomial logistic regression models were used to identify variables that were independently associated with the odds of selecting a medication from each diabetes drug class. All patient-level, prescriber-level, and health plan-level variables were included as covariates in each model. We present the predicted probabilities produced by marginal standardization, where the probabilities are proportionally adjusted according to the weight for each level of the confounding factors.[5]

RESULTS

Prescribing volume and patterns of select diabetes medications

Between January 2011 and June 2015, 77 744 patients had evidence of metformin monotherapy followed by a first fill for one of the six second-line T2D drug classes. SFUs were prescribed most frequently, accounting for almost half (47.4%) of all prescriptions (98.9% of which were sulfonylureas; 1.1% were meglitinides); TZDs were prescribed least, accounting for <5% of all prescriptions. However, the relative contribution of each drug class to total prescribing changed considerably over the 5-year period (figure 1). Between 2011 and 2012, DPP4 prescribing increased from 19% to 32% of overall second-line drug starts, with concomitant reductions in both SFUs and TZDs. Since entering the market in 2013, the

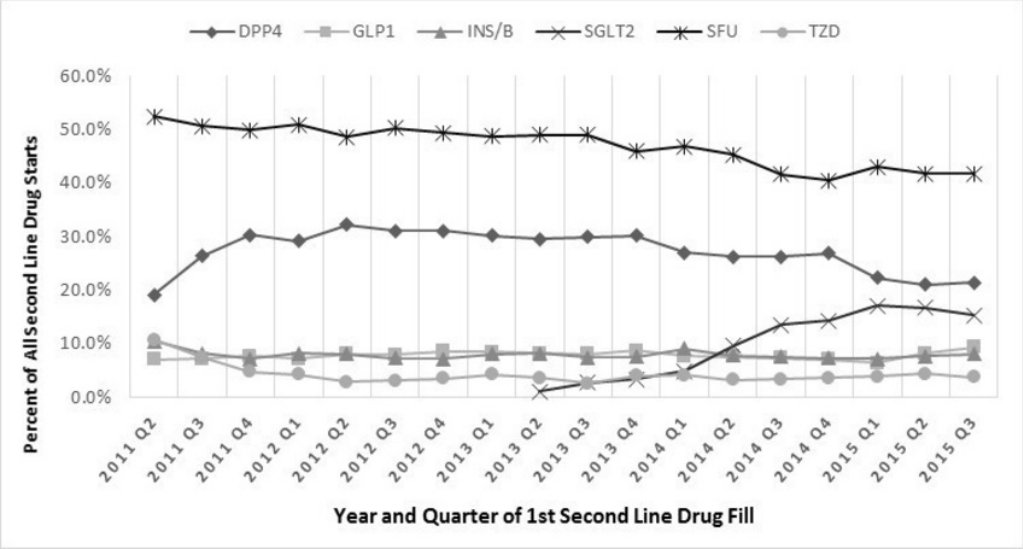

Figure 1 Trends in the relative contribution of each second-line diabetes medication class, by quarter, as a percent of all second-line prescribing, 2011–2015. Each line represents a quarterly time trend for the percent of all second-line drug starts (ie, all six categories combined) that were contributed by each class; values for all six classes in each quarter total to 100%. DPP4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptide-1 receptor agonists; INS/B, long-acting or intermediate-acting insulin given as a basal (rather than mealtime) injection; SGLT2, sodium-glucose cotransporter 2 inhibitors; SFU, sulfonylurea or meglitinides; TZD, thiazolidinediones.

percentage of overall prescribing attributable to SGLT2s increased from 0% to about 15%–17%, with concomitant decreases in every other drug class except TZDs.

Unadjusted percentages of drug prescribing across select patient, provider, and health plan characteristics are displayed in table 2. The online supplementary appendix also includes unadjusted values for all other covariates examined. Slightly more than 43% of the study population were women, about 60% were between ages 45 and 64, and about 27% were believed to be black or Hispanic/Latino. About 85% of the population were in commercial health plans; 15% were in Medicare Advantage plans. Just more than half of plans had a POS structure, and 28% were HMOs. A majority of prescriptions were written by either a family medicine (44%) or general internal medicine (32%) provider; only 7% of prescriptions were from an endocrinologist. There were statistically significant differences across the six drug classes in every patient, prescriber, and health plan characteristic examined.

Adjusted probabilities of second-line medication prescribing for T2D

Table 3 shows the fully adjusted prescribing probabilities for each of the six drug classes, both overall, and within strata of patient, prescriber, and health plan characteristics. In adjusted models, the rank ordering of T2D drug class prescribing, from highest to lowest probability, was similar to unadjusted findings: SFUs were the most common, followed by DPP4s, GLP1s, INS/Bs, SGLT2s, and TZDs.

Adjusted associations of T2D medication prescribing with patient characteristics

SFUs remained the most common drug class across all patient-level characteristics. However, several characteristics were associated with significant differences in the selection of each class. For example, men received a GLP1 less often than women (5.9% vs 10.1%, difference −4.1%, 95% CI (−4.7% to −3.6%)) but were more likely than women to receive SFUs or TZDs. With advancing age, there was an increase in DPP4 and SFU prescribing, with a decrease in GLP1 and INS/B prescribing; 11.8% of persons <35 years of age received a GLP1, compared with only 5.6% of individuals 64–75 years of age (difference −6.2%, 95% CI (−8.2% to −4.2%)) and only 3.4% of individuals ≥75 years (difference −8.4%, 95% CI (−10.5% to −6.3%)). Recent hospitalization was associated with a higher probability of receiving INS/B (difference 5.3%, 95% CI (4.4% to 6.2%)) but relatively lower probabilities of DPP4s, GLP1s, or SGLT2s. When compared with patients with a prior A1c <8%, patients with A1c values ≥10% had a higher probability of receiving INS/B (difference 8.5%, 95% CI (6.4% to 10.7%)) and SFUs (difference 7.0%, 95% CI (3.7% to 10.3%), and had lower probabilities of receiving DPP4s, GLP1s, SGLT2s, or TZDs. Finally, having a prior obesity diagnosis code was associated with higher probabilities of receiving GLP1s (difference 3.9%, 95% CI (3.2% to 4.6%)) and SGLT2s (difference 1.0%, 95% CI (0.6% to 1.5%)), with lower probabilities of INS/B, SFUs, or TZDs.

Adjusted associations of T2D medication prescribing with provider characteristics

When compared with patients who were prescribed their T2D medication by a family physician, those with an endocrinologist prescriber were more likely to receive INS/B (10.1% vs 7.8%, difference 2.3%, 95% CI (0.7% to 3.8%)) or GLP1s (10.6% vs 7.2%, difference 3.3%, 95% CI (2.0% to 4.6%)) but were less likely to receive SGLT2s, SFUs, or TZDs. Similar differences in prescribing patterns were observed comparing general internists and endocrinologists. Even after adjusting for the prescriber's specialty type, providers who wrote T2D prescriptions for a higher percentage of their patients were more likely to prescribe GLP1s than were providers with proportionately lower rates of diabetes drug prescribing (difference between highest and lowest quartile, 4.2%, 95% CI (3.4% to 5.0%). Providers with a relatively high level of recent prescribing for a particular drug class had a higher probability of selecting a T2D medication within that same class. For example, patients who received their medication from a provider who was above the 75th percentile of recent prescribing for DPP4s had a 41% probability of receiving a DPP4, compared with only 19% of patients seeing a provider with no recent DPP4 prescribing. Similar patterns were observed for all six classes. Finally, geographical location was associated with choice of drug class. For example, compared with other regions, patients seeing prescribers in the Northeast were more likely to receive a DPP4 and less likely to receive an SFU than were patients in all other regions.

Adjusted associations of T2D medication prescribing with health plan characteristics

After adjustment for other patient, prescriber, and health plan differences, individuals in a Medicare Advantage plan were more likely than those in a commercial health plan to receive INS/B (difference 3.1%, 95% CI (1.5% to 4.6%)) and SFUs (difference 5.1%, 95% CI (2.8% to 7.4%)), and were less likely to receive DPP4s, GLP1s, or SGLT2s. The 'richness' of health coverage (ie, percentage of total healthcare costs that were paid by the patient) was also associated with T2D drug selection; compared with patients in health plans in the lowest quartile of out-of-pocket costs, patients in plans in the highest quartile were more likely to receive DPP4s (difference 2.6%, 95% CI (1.1% to 4.1%)) and were less likely to receive INS/B (difference −1.1%, 95% CI (−2.1% to −0.3%)) or SFUs (difference −2.4%, 95% CI (−4.0% to −0.7%)). No clear associations were observed with the health plan structure (eg, HMO vs PPO plans).

CONCLUSIONS

Despite the emergence of newer classes of T2D medications that do not cause weight gain or hypoglycemia,

Table 2 Unadjusted patient, prescriber, and health plan characteristics for each second-line diabetes medication group*

	Total	DPP4	GLP1	INS/B	SGLT2	SFU	TZD
N (%)	77 744 (100)	20 709 (100)	6082 (100)	6350 (100)	3995 (100)	36 856 (100)	3752 (100)
Women	33 539 (43.1)	8924 (100)	3634 (100)	2817 (44.4)	1756 (44.0)	14 978 (40.6)	1427 (38.0)
Age category							
18–44	10 387 (13.4)	2652 (12.8)	1237 (20.3)	1013 (15.9)	733 (18.4)	4356 (11.8)	400 (10.7)
45–64	47 409 (61.0)	13 209 (63.8)	4057 (66.7)	3727 (58.7)	2908 (72.8)	21 409 (58.1)	2089 (55.7)
65+	19 949 (25.7)	4846 (23.4)	788 (12.9)	1610 (25.3)	354 (8.9)	11 090 (30.1)	1263 (33.7)
Race/Ethnicity†							
Black	8451 (10.9)	2247 (10.9)	644 (10.6)	827 (13.0)	398 (10.0)	4032 (10.9)	301 (8.0)
Hispanic	12 999 (16.7)	3318 (16.0)	715 (11.8)	1046 (16.5)	592 (14.8)	6527 (17.7)	801 (21.4)
Non-Hispanic white	48 022 (61.8)	12 734 (61.5)	4315 (71.0)	3930 (61.9)	2667 (66.8)	22 217 (60.3)	2159 (57.5)
Unknown/Other	8280 (10.7)	2413 (11.7)	408 (6.7)	547 (8.6)	338 (8.5)	4084 (11.1)	491 (13.1)
Most recent A1c value							
<8%	10 021 (12.9)	3378 (16.3)	1246 (20.5)	402 (6.3)	864 (21.6)	3630 (9.9)	503 (13.4)
8%–10%	10 433 (13.4)	3434 (16.6)	635 (10.4)	444 (7)	725 (18.2)	4747 (12.9)	445 (11.9)
>10%	7184 (9.2)	1779 (8.6)	381 (6.3)	934 (14.7)	431 (10.8)	3380 (9.2)	274 (7.3)
Result not available‡	50 114 (64.5)	12 119 (58.5)	3820 (62.8)	4570 (72)	1975 (49.4)	25 095 (68.1)	2530 (67.4)
Obesity diagnosis code	16 855 (21.7)	4376 (21.1)	2101 (34.5)	1193 (18.8)	1405 (35.2)	7205 (19.6)	574 (15.3)
Recent hospitalization	12 836 (16.5)	2916 (14.1)	810 (13.3)	1674 (26.4)	234 (5.9)	6597 (17.9)	601 (16.0)
Recent healthcare cost level							
Below median	37 138 (47.8)	8532 (41.2)	2202 (36.2)	3248 (51.2)	1699 (42.5)	19 464 (52.8)	1998 (53.3)
50th–75th percentile	19 094 (24.6)	5475 (26.4)	1491 (24.5)	1472 (23.2)	1052 (26.3)	8687 (23.6)	916 (24.4)
>75th percentile	21 512 (27.7)	6704 (32.3)	2389 (39.3)	1630 (25.6)	1244 (31.1)	8706 (23.6)	838 (22.4)
Charlson Comorbidity Score§							
0 (lowest)	3732 (4.8)	656 (3.2)	407 (6.7)	430 (6.8)	83 (2.1)	1880 (5.1)	277 (7.4)
1	42 767 (55.0)	11 823 (57.1)	3339 (54.9)	3194 (50.3)	2205 (55.2)	20 157 (54.7)	2055 (54.8)
2 or 3	20 213 (26.0)	5306 (25.6)	1641 (27.0)	1729 (27.2)	1130 (28.3)	9498 (25.8)	910 (24.3)
4+ (highest)	11 032 (14.2)	2924 (14.1)	695 (11.4)	997 (15.7)	577 (14.4)	5326 (14.5)	510 (13.6)
Census region location							
Northeast	9189 (11.8)	3262 (15.8)	869 (14.3)	643 (10.1)	448 (11.2)	3649 (9.9)	319 (8.5)
Midwest	16 793 (21.6)	3614 (17.5)	1268 (20.9)	1514 (23.8)	841 (21.1)	8856 (24.0)	703 (18.7)
South	32 528 (41.8)	9261 (44.7)	2930 (48.2)	2500 (39.4)	2120 (53.1)	14 355 (39.0)	1365 (36.4)
West	19 234 (24.7)	4573 (22.1)	1015 (16.7)	1693 (26.7)	586 (14.7)	9999 (27.1)	1365 (36.4)
Clinical discipline							
Endocrinologist	5294 (6.8)	1561 (7.5)	1250 (20.6)	581 (9.2)	379 (9.5)	1382 (3.8)	144 (3.8)
Family medicine	33 858 (43.6)	8822 (42.6)	2078 (34.2)	2556 (40.3)	1767 (44.2)	16 677 (45.3)	1955 (52.1)

Continued

Table 2 Continued

	Total	DPP4	GLP1	INS/B	SGLT2	SFU	TZD
Internal medicine	24 583 (31.6)	6799 (32.8)	1599 (26.3)	1843 (29.0)	1047 (26.2)	12 255 (33.3)	1042 (27.8)
Nurse/Physician assistant	5893 (7.6)	1595 (7.7)	611 (10.1)	539 (8.5)	431 (10.8)	2477 (6.7)	238 (6.3)
Other/Missing	8116 (10.4)	1934 (9.3)	544 (8.9)	831 (13.1)	371 (9.3)	4062 (11)	373 (9.9)
Insurance category							
Commercial	66 168 (85.1)	18 464 (89.2)	5786 (95.1)	5255 (82.8)	3912 (97.9)	29 839 (81)	2915 (77.7)
Medicare	11 576 (14.9)	2245 (10.8)	296 (4.9)	1095 (17.2)	83 (2.1)	7017 (19)	837 (22.3)
Health plan structure							
Indemnity plan	809 (1.0)	176 (0.9)	27 (0.4)	82 (1.3)	25 (0.6)	453 (1.2)	44 (1.2)
Preferred provider organization	1594 (2.1)	404 (2.0)	133 (2.2)	132 (2.1)	78 (2.0)	763 (2.1)	84 (2.2)
Exclusive provider organization	6740 (8.7)	1862 (9.0)	596 (9.8)	517 (8.1)	414 (10.4)	3041 (8.3)	314 (8.4)
Point of service plan	44 089 (56.7)	12 111 (58.5)	4001 (65.8)	3542 (55.8)	2784 (69.7)	19 759 (53.6)	1896 (50.5)
Health maintenance organization	21 753 (28.0)	5229 (25.3)	1052 (17.3)	1873 (29.5)	573 (14.3)	11 724 (31.8)	1302 (34.7)
Other	2752 (3.5)	928 (4.5)	273 (4.5)	204 (3.2)	121 (3.0)	1117 (3.0)	112 (3.0)

*Race and ethnicity are not routinely collected in health plan administrative data sources but have been imputed by the data vendor from regional and other individual characteristics.
†Lab values are not routinely available in health plan administrative data sources unless submitted by the laboratory vendor as part of their contract with the health payer; for these data, 38% of submitted laboratory claims nationally included a result.
‡Reflects the number of chronic disease diagnoses demonstrated in the claims record; higher numbers reflect higher comorbidity.
§$p<0.001$ for every patient, prescriber, and health plan characteristic included in the table, using a χ^2test for categorical data comparing type 2 diabetes medication classes.
DPP4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptide-1 receptor agonists; INS/B, long-acting or intermediate-acting insulin given as a basal (rather than mealtime) injection; SGLT2, sodium-glucose cotransporter 2 inhibitors; SFU, sulfonylurea or meglitinides; TZD, thiazolidinediones.

Table 3 Adjusted percentages of patients receiving prescriptions for each second-line diabetes drug class

	DPP4		GLP1		INS/B		SGLT2		SFU		TZD	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Overall	26.6	26.5 to 26.7	7.8	7.7 to 7.9	8.2	8.1 to 8.2	5.1	5.1 to 5.2	47.4	47.3 to 47.5	4.8	4.8 to 4.9
Individual characteristics												
Gender												
Women	26.7	26.1 to 27.3	10.1	9.7 to 10.5	8.4	8.0 to 8.8	5.2	4.9 to 5.5	45.3	44.6 to 46.0	4.3	4.0 to 4.6
Men	26.7	26.1 to 27.3	5.9	5.6 to 6.3	8.0	7.6 to 8.4	5.1	4.8 to 5.4	49.0	48.4 to 49.7	5.3	5.0 to 5.6
Age												
18–34	23.9	21.4 to 26.4	11.8	10.3 to 13.3	12.4	10.7 to 14.1	4.9	3.7 to 6.0	43.0	40.3 to 45.8	4.0	2.8 to 5.2
35–44	25.9	23.8 to 27.9	10.6	9.3 to 12.0	9.8	8.3 to 11.4	5.3	4.5 to 6.2	43.9	41.5 to 46.2	4.5	3.5 to 5.5
45–54	26.7	24.7 to 28.6	9.1	7.7 to 10.4	8.6	7.1 to 10.1	5.4	4.7 to 6.2	45.6	43.5 to 47.8	4.6	3.7 to 5.6
55–64	26.6	24.7 to 28.6	7.3	6.0 to 8.6	8.4	6.9 to 9.9	5.2	4.4 to 5.9	47.5	45.3 to 49.7	5.0	4.0 to 6.0
65–74	27.8	25.8 to 29.9	5.6	4.2 to 6.9	7.0	5.5 to 8.6	4.5	3.6 to 5.4	50.1	47.8 to 52.4	5.0	4.0 to 6.0
75+	28.0	25.5 to 30.5	3.4	1.9 to 4.9	6.6	4.9 to 8.3	2.3	1.2 to 3.5	54.5	51.8 to 57.3	5.2	4.0 to 6.3
Recent healthcare cost level												
Low (below median)	24.6	23.3 to 26.0	6.6	5.8 to 7.4	8.4	7.5 to 9.2	4.8	4.1 to 5.5	50.5	49.0 to 52.0	5.1	4.5 to 5.8
High (>95thpercentile)	29.6	28.3 to 31.0	10.2	9.4 to 11.1	8.3	7.4 to 9.1	6.0	5.3 to 6.7	41.5	40.1 to 43.0	4.3	3.6 to 4.9
Recent hospitalization	23.7	22.8 to 24.5	7.1	6.6 to 7.6	12.6	12.0 to 13.2	3.6	3.2 to 4.1	48.7	47.7 to 49.6	4.4	4.0 to 4.7
Charlson Comorbidity Score*												
0 (lowest)	20.4	18.8 to 22.0	12.1	10.9 to 13.3	12.3	11.0 to 13.5	3.4	2.7 to 4.2	46.3	44.4 to 48.1	5.5	4.7 to 6.3
1	27.4	24.4 to 30.4	7.8	5.5 to 10.1	7.5	5.2 to 9.9	5.3	3.8 to 6.8	47.2	43.7 to 50.6	4.8	3.3 to 6.2
2 or 3	25.9	22.8 to 29.0	7.8	5.4 to 10.1	8.5	6.0 to 10.9	5.2	3.6 to 6.7	47.9	44.4 to 51.5	4.8	3.3 to 6.3
4+ (highest)	27.0	23.7 to 30.2	6.6	4.2 to 9.0	8.7	6.2 to 11.2	4.8	3.2 to 6.4	48.0	44.3 to 51.7	4.9	3.3 to 6.5
Diagnosis of obesity†	25.7	25.0 to 26.5	10.8	10.3 to 11.3	6.9	6.4 to 7.3	5.9	5.5 to 6.2	46.5	45.6 to 47.3	4.3	3.9 to 4.7
Most recent A1c value												
<8%	31.3	29.3 to 33.3	10.4	9.2 to 11.6	4.5	3.1 to 5.8	6.1	5.3 to 7.0	41.9	39.7 to 44.2	5.7	4.6 to 6.7
8%–10%	31.2	29.2 to 33.2	6.4	5.3 to 7.5	4.6	3.2 to 5.9	5.3	4.5 to 6.1	47.8	45.6 to 50.0	4.7	3.7 to 5.7
>10%	23.8	21.7 to 25.8	5.6	4.4 to 6.7	13.0	11.3 to 14.7	4.6	3.7 to 5.4	48.9	46.5 to 51.3	4.2	3.1 to 5.2
Result not available‡	25.2	24.2 to 26.2	7.9	7.3 to 8.5	8.9	8.0 to 9.7	4.9	4.5 to 5.4	48.3	47.1 to 49.5	4.8	4.3 to 5.3
Diagnosis of poor control§	27.5	26.8 to 28.1	7.6	7.2 to 8.0	9.7	9.3 to 10.1	5.1	4.8 to 5.4	45.7	45.0 to 46.4	4.5	4.2 to 4.8
Prescriber characteristics												
Clinical discipline												
Endocrinology	28.1	26.4 to 29.8	10.6	9.6 to 11.5	10.1	8.9 to 11.3	4.6	3.9 to 5.3	43.2	41.2 to 45.2	3.5	2.7 to 4.3
Family practice	26.6	25.1 to 28.2	7.2	6.4 to 8.1	7.8	6.8 to 8.9	5.5	4.9 to 6.1	47.2	45.4 to 49.0	5.5	4.9 to 6.2
General/Internal	27.1	25.5 to 28.6	7.4	6.6 to 8.3	7.8	6.8 to 8.8	5.1	4.5 to 5.7	48.5	46.7 to 50.2	4.2	3.6 to 4.9
Proportion of patients for which type 2 diabetes drugs were prescribed¶												
Lowest quartile	27.7	26.8 to 28.7	5.7	5.1 to 6.3	8.2	7.6 to 8.8	4.6	4.2 to 5.1	49.1	48.0 to 50.1	4.7	4.2 to 5.1

Continued

Table 3 Continued

	DPP4		GLP1		INS/B		SGLT2		SFU		TZD	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Highest quartile	25.1	24.2 to 26.1	9.9	9.3 to 10.5	8.9	8.3 to 9.6	5.3	4.9 to 5.8	45.3	44.2 to 46.4	5.4	4.9 to 5.9
Recent prescribing behavior												
Top quartile of DPP4 use	41.1	39.4 to 42.8	7.4	6.4 to 8.5	6.6	5.5 to 7.6	5.2	4.5 to 6.0	35.5	33.7 to 37.3	4.2	3.4 to 4.9
Any GLP1 use	28.1	26.5 to 29.6	14.7	13.5 to 15.9	8.5	7.5 to 9.6	5.4	4.7 to 6.1	38.8	37.1 to 40.6	4.5	3.8 to 5.3
Top quartile of INS/B use	25.5	23.7 to 27.2	7.5	6.5 to 8.6	10.3	9.2 to 11.4	5.0	4.2 to 5.8	47.6	45.7 to 49.5	4.0	3.2 to 4.9
Any SGLT2 use	28.2	26.9 to 29.4	7.8	7.1 to 8.4	8.6	7.8 to 9.5	11.8	11.2 to 12.4	38.5	37.1 to 39.8	5.1	4.4 to 5.8
Top quartile of SFU use	20.2	18.3 to 22.0	4.9	3.7 to 6.1	7.0	5.8 to 8.2	3.7	2.8 to 4.6	60.9	58.9 to 62.8	3.3	2.3 to 4.3
Top quartile of TZD use	26.9	25.3 to 28.5	7.8	6.8 to 8.8	7.6	6.6 to 8.6	5.4	4.5 to 6.2	42.2	40.4 to 43.9	10.1	9.1 to 11.2
Census region where healthcare was received												
Northeast	31.6	30.4 to 32.9	8.0	7.3 to 8.8	7.4	6.6 to 8.1	5.0	4.4 to 5.6	44.0	42.6 to 45.3	4.0	3.4 to 4.6
Midwest	23.6	22.4 to 24.9	7.4	6.7 to 8.1	8.5	7.8 to 9.2	4.8	4.2 to 5.4	51.1	49.8 to 52.4	4.5	3.9 to 5.1
South	26.8	25.7 to 28.0	8.1	7.4 to 8.7	7.9	7.2 to 8.6	5.6	5.0 to 6.1	47.4	46.2 to 48.6	4.3	3.7 to 4.8
West	26.4	25.2 to 27.7	7.7	6.9 to 8.4	8.8	8.0 to 9.5	4.5	3.9 to 5.1	46.3	45.0 to 47.7	6.3	5.7 to 6.9
Insurance and health plan characteristics												
Insurance category												
Commercial	27.4	26.0 to 28.8	8.0	7.1 to 8.9	7.8	6.7 to 8.9	5.2	4.5 to 6.0	46.8	45.2 to 48.4	4.8	4.1 to 5.5
Medicare	22.8	21.4 to 24.2	6.2	5.3 to 7.1	10.9	9.8 to 12.0	2.9	2.2 to 3.6	52.0	50.3 to 53.6	5.3	4.5 to 6.0
Health plan structure												
Indemnity plan	24.0	20.7 to 27.2	6.8	4.4 to 9.3	9.8	7.6 to 12.1	6.3	4.0 to 8.5	48.1	44.5 to 51.8	5.0	3.4 to 6.5
Preferred provider organization	25.3	23.0 to 27.5	8.1	6.8 to 9.5	8.1	6.6 to 9.6	5.4	4.2 to 6.5	47.4	44.8 to 49.9	5.7	4.5 to 7.0
Exclusive provider organization	25.2	22.9 to 27.4	7.4	6.1 to 8.8	8.3	6.8 to 9.8	4.8	3.7 to 6.0	49.0	46.5 to 51.6	5.2	3.9 to 6.5
Point of service plan	26.9	25.8 to 28.0	8.1	7.5 to 8.7	8.1	7.4 to 8.9	5.3	4.9 to 5.8	46.8	45.6 to 48.0	4.8	4.2 to 5.4
Health maintenance organization	26.8	25.5 to 28.1	7.2	6.5 to 7.9	8.2	7.3 to 9.1	4.5	3.9 to 5.0	48.5	47.1 to 50.0	4.8	4.1 to 5.5
Richness of health plan benefits based on out-of-pocket costs as percent of total costs for all enrollees in the same plan**												
Lowest quartile cost share	24.3	23.2 to 25.5	7.4	6.7 to 8.1	9.1	8.4 to 9.8	5.1	4.5 to 5.7	49.2	48.0 to 50.5	4.9	4.3 to 5.4
Highest quartile cost share	26.9	26.0 to 27.8	7.7	7.1 to 8.3	7.9	7.3 to 8.5	5.5	5.0 to 5.9	46.9	45.8 to 47.9	5.2	4.7 to 5.6

All estimates are adjusted for all other covariates in the table; some covariate categories are not included here for space constraints; please see online supplementary appendix for complete classification and adjusted estimates for each variable.
*Generally reflects a count of comorbid conditions (higher numbers reflect greater comorbidity).
†Reflects a prior encounter with an obesity diagnosis code (see online supplementary appendix for details).
‡Lab values are not routinely available in health plan administrative data sources unless submitted by the laboratory vendor as part of their contract with the health payer; for these data, 38% of submitted laboratory claims nationally included a result.
§Reflects a prior encounter for uncontrolled or poorly controlled diabetes (see online supplementary appendix for details).
¶For percentage of prescriptions that were for diabetes: lowest quartile=≤7.7% of patients; highest quartile=≥20.0% of patients. For percent of patient total costs that were out-of-pocket costs: lowest quartile=≤6.1% of total costs; highest quartile=≥11.7% of total costs.
**The highest quartile of health plan "richness" corresponds to the plans with the *lowest* median out of pocket costs, calculated as the percentage of total healthcare costs paid by the patient, rather than by the plan, for all patients in the same plan.
DPP4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptide-1 receptor agonists; INS/B, long-acting or intermediate-acting insulin given as a basal (rather than mealtime) injection; SGLT2, sodium-glucose cotransporter 2 inhibitors; SFU, sulfonylurea or meglitinides; TZD, thiazolidinediones.

SFUs remain the most commonly prescribed second-line diabetes drug class. Since 2013, prescribing has increased most for SGLT2s, with corresponding decreases in every other drug class except TZDs. Although this demonstrates changes in T2D medication prescribing, SFUs were still selected for about 42% of patients in 2015. Because SFUs have been on the market since the 1950s, prescribers may have more familiarity with how to initiate these medications and more confidence that they are aware of potential side effects. SFUs also cost less and have greater glucose-lowering effects than do many newer medication alternatives, possibly also contributing to their sustained use.

Our analysis uncovered several associations among patient-level, prescriber-level, and health plan-level characteristics with the selection of second-line T2D medications. For example, SFU selection increased for patients who were over age 65 and those with higher past A1c results. Initiation of basal insulin increased for patients who were younger, non-obese, and who had a recent hospitalization or prior high A1c result. Initiation of a GLP1 was higher for patients who were younger, female, obese, or who had lower past A1c test results. Selection of DPP4s increased for patients ≥45 years of age, as well as for those with higher comorbidity and lower past A1c results. SGLT2 selection increased for patients who were <75 years of age and who had lower past A1c results.

Many of these patterns seem appropriate and may reflect some amount of patient-centered prescribing.[6] For example, SFUs and basal insulin have greater glucose-lowering efficacy but also have concerns for weight gain and hypoglycemia, which may diminish prescribing among patients who are obese or who have lower A1c results. By contrast, DPP4, GLP1, and SGLT2 agents are often viewed to have lower glucose-lowering efficacy, minimal threat of hypoglycemia, and do not promote weight gain, making them more favorable for patients who have lower A1c tests or are more concerned about weight gain. One unanticipated finding was that adults >65 years and those on Medicare plans were most likely to receive SFUs. Two of the drugs in this class (glyburide and chlorpropamide) are on the American Geriatric Society's Beers' list of medications to avoid because of safety concerns related to unpredictable and severe hypoglycemia in older adults.[7 8] About 70% of new SFU drug starts among adults >65 years were for a long-acting SFUs, and 21% included one of the two drugs on the Beers' list; only 1.4% were for meglitinides, which generally have lower risk for hypoglycemia. This finding represents an opportunity for further research as well as for quality improvement initiatives to ensure safe prescribing of antiglycemic medications in older adults.

Our analysis found that a provider's recent prescribing of a particular drug class had a strong relationship with subsequent drug selection, suggesting that repetition and familiarity initiating a particular drug may be important determinants of drug selection. This may not be surprising, but it underscores the risk of industry activities to influence prescriber behavior in ways that may not be evidence-based, as well as the importance of quality assurance efforts that insure all prescribers have a balanced approach to prescribing. Another interesting pattern was the relationship between having proportionately higher levels of diabetes prescribing (or being an endocrinologist) and the greater use of GLP1s. Although one might speculate that providers with more patients with diabetes are simply more likely to prescribe newer medications, a similar pattern was not observed for SGLT2 inhibitors. One explanation for greater prescribing of injectable medications might also be that higher volume providers have more capacity to provide patients with additional education when starting these medications, as well as familiarity with how to prescribe injection supplies.

Patients in health plans with lower out-of-pocket costs were generally less likely to receive newer or costlier second-line medications, such as DPP4s, GLP1s, and SGLT2s, and were more likely to receive drugs that are generally cheaper or have been on the market longer, such as SFUs and basal insulin. It is possible that health plans with lower cost sharing are more likely to impose formulary restrictions or tiered medication copays that offer SFUs at a lower cost to patients, thereby driving selection of those medications. However, the lack of a clear relationship between T2D drug selection and health plan structure (eg, HMO vs PPO) may suggest that other forms of drug and utilization management strategies used by plans may yield inconsistent effects on prescribing. This deserves further research.

Limitations

Our study has notable limitations. First, the reliance on administrative data could lead to misclassification of the timing of second-line treatment. For example, some manufacturers offer coupons to promote the use of newer medications, which may make it difficult to determine the timing of a drug start based on the first submitted pharmacy claim. This also could result in underestimation of the prevalence of some newer medications. Another limitation is that we did not have information about provider characteristics, such as age or date of last board certification, which may relate to their selection of medications. Finally, the observational study design limits our ability to know if associations are causal; additional longitudinal research is needed to determine if more frequent use of certain medications has any impact, good or bad, on important health or economic outcomes.

Our study provides important information about the resilience of sulfonylureas and recent emergence of SGLT2 inhibitors as second-line agents for the management of T2D when metformin is no longer sufficient. In general, select health plan, prescriber, and patient characteristics were associated with the probability that a particular second-line medication was selected. This information should cause health plan administrators to

think carefully about all potential effects of policies that restrict formularies or shift medication costs to patients. These findings also will be valuable for the design of future research that compares potential benefits and harms of these medications on important health and economic outcomes.

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