Determinants of Adherence to Diabetes Medications: Findings From a Large Pharmacy Claims Database

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OBJECTIVE

Adults with diabetes typically take multiple medications for hyperglycemia, diabetes-associated conditions, and other comorbidities. Medication adherence is associated with improved outcomes, including reduced health care costs, hospitalization, and mortality. We conducted a retrospective analysis of a large pharmacy claims database to examine patient, medication, and prescriber factors associated with adherence to antidiabetic medications.

RESEARCH DESIGN AND METHODS

We extracted data on a cohort of >200,000 patients who were treated for diabetes with noninsulin medications in the second half of 2010 and had continuous prescription benefits eligibility through 2011. Adherence was defined as a medication possession ratio ≥0.8. We used a modified adherence measure that accounted for switching therapies. Logistic regression analysis was performed to determine factors independently associated with adherence.

RESULTS

Sixty-nine percent of patients were adherent. Adherence was independently associated with older age, male sex, higher education, higher income, use of mail order versus retail pharmacies, primary care versus nonendocrinology specialist prescribers, higher daily total pill burden, and lower out-of-pocket costs. Patients who were new to diabetes therapy were significantly less likely to be adherent.

CONCLUSIONS

Several demographic, clinical, and potentially modifiable system-level factors were associated with adherence to antidiabetic medications. Patients typically perceived to be healthy (those who are younger, new to diabetes, and on few other medications) may be at risk for nonadherence. For all patients, efforts to reduce out-of-pocket costs and encourage use of mail order pharmacies may result in higher adherence.

Adults with type 2 diabetes are often prescribed multiple medications to treat hyperglycemia, diabetes-associated conditions such as hypertension and dyslipidemia, and other comorbidities. Medication adherence is an important determinant of outcomes in patients with chronic diseases. For those with diabetes, adherence to medications is associated with better control of intermediate risk factors (1–4), lower odds of hospitalization (3,5–7), lower health care costs (5,7–9), and lower

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mortality (3,7). Estimates of rates of adherence to diabetes medications vary widely depending on the population studied and how adherence is defined. One review found that adherence to oral antidiabetic agents ranged from 36 to 93% across studies and that adherence to insulin was ~63% (10).

Although much is known about the adverse "downstream" effects of medication nonadherence, the determinants of medication adherence are less well defined. Most studies have looked at either individual-level or system-level factors independently, whereas few studies have used large generalizable cohorts. Using a large pharmacy claims database, we assessed determinants of adherence to oral antidiabetic medications in >200,000 U.S. adults with type 2 diabetes. We looked at a wide range of variables and categorized those potential determinants into patient factors, prescriber factors, and factors related to the prescribed medication or the prescription system.

RESEARCH DESIGN AND METHODS

Data Sources

Data were extracted from the information warehouse of Medco Health Solutions, a large U.S. managed-care company that provided pharmacy management services to a range of clients, including employers and health plans. (Medco Health Solutions merged with another large pharmacy benefit management company, Express Scripts, in April 2012.) The information warehouse is a data repository that includes demographic, eligibility, and pharmacy claims information related to the dispensing event. The sample includes patients from all 50 states and the larger U.S. territories including Puerto Rico, the Virgin Islands, and Guam. Fifty-three percent of the patients received their pharmacy benefits from a health plan, 17% labor and government, 19% large employer groups, 2% Medicare, and 9% small business groups and others.

Using prescription claims from the database, we extracted drug utilization data and determined study eligibility. Eligibility was based on drug type, benefits, and prescription history. We selected a cohort of members treated for diabetes with noninsulin medications (oral agents or GLP-1 agonists) in the second half of 2010 who had continuous prescription benefits eligibility through 2011. Each patient was followed for 12 months from their index diabetes claim date identified during the 6-month targeting period. From each patient's prescription history, we collected the date the prescription was filled, how many days the supply would last, the National Drug Code number, and the drug name. For patients included in the analysis, household income and education level were provided by a commercial vendor and appended to the file.

Given the difficulty in assessing insulin adherence with measures such as medication possession ratio (MPR), we excluded patients using insulin when defining the cohort. To simplify the analyses with respect to distinguishing medication switches and additions, we also restricted the analysis to patients using no more than two antidiabetic medications during the targeting period. This decision had minimal impact on sample size, with <3.5% of patients being on three or more medications for diabetes.

Predictors and Outcomes of Interest

Predictor variables were defined a priori and grouped into three categories: *1*) patient factors including age, sex, education, income, region, past exposure to therapy (new to diabetes therapy vs. continuing therapy), and concurrent chronic conditions; *2*) prescription factors including refill channel (retail vs. mail order), total pill burden per day, and out of pocket costs; and *3*) prescriber factors including age, sex, and specialty. Pill burden was defined for all oral maintenance medications (diabetes and nondiabetes) filled and was computed by multiplying the average number of maintenance medications per month by the average number of oral maintenance pills per day, which was then converted to a 30-day period. Patient out-of-pocket prescription costs per month were estimated by summing the total copays and deductibles for each chronic maintenance prescription, dividing by the number of days supply (resulting in the cost per day), and then multiplying by 30 to reflect a 30-day period. Patients filling one or more of their diabetes medications by mail were considered mail channel.

Our primary outcome of interest was adherence to noninsulin antidiabetic medications. To assess adherence, we calculated an MPR for each patient. The ratio captures how often patients refill their medications and is a standard metric that is consistent with the National Quality Forum's measure of adherence to medications for chronic conditions. MPR was defined as the proportion of days a patient had a supply of medication during a calendar year or equivalent period. We considered patients to be adherent if their MPR was 0.8 or higher, implying that they had their medication supplies for at least 80% of the days. An MPR of 0.8 or above is a well-recognized index of adherence (11,12). Studies have suggested that patients with chronic diseases need to achieve at least 80% adherence to derive the full benefits of their medications (13).

After establishing a patient's adherence status, we then determined whether a patient was persistent, that is whether they had not discontinued or had at least a 45-day gap in their targeted therapy. We used a modified adherence measure, which was meant to account for changing diabetes drug classes, in this analysis. For the modified measure, patients with an MPR <0.80 were reclassified as adherent if they were persistent (<45-day gap) and subsequently filled a diabetes therapy (including insulin) different than their index regimen.

Patients on two diabetes agents were credited for days with either medication. This method conservatively avoids misclassifying patients who may have switched from one class to another, which can happen when averaging MPRs for each class. Of the 218,384 diabetic patients, 59,035 (27.0%) were taking more than one medication to treat their diabetes and, using this methodology, were considered adherent to their diabetes therapy. Of these patients, 2,706 (4.5% of those on dual therapy considered adherent by our methodology; 1.2% of the total population) had an MPR <0.8 for at least one of their medications; thus, their overall adherence could be overestimated.

Analyses

We used a logistic regression analysis to examine the independent effects of patient, medication, and prescriber variables on diabetes medication adherence. For the logistic model, we used a stepwise regression, with variables selection for entry equal to univariate *P* of 0.05 or

less. The C-statistic, an indicator for model fit, was 0.73, suggesting reasonable fit. The number of chronic disease conditions and patient total pill burden were highly positively correlated, and thus only patient pill burden was considered in the multivariate analysis. Missing values for a given variable were assigned the value of the mode.

We considered findings to be statistically significant if the *P* value for the relationship was <0.05. Precision of estimates was assessed by 95% CIs. All statistical analyses were performed using SAS software version 9.3 (14).

RESULTS

There were 218,384 patients who met the criteria for inclusion. Table 1 describes the analyzed population. Sixty-nine percent met the criteria for adherence using the modified definition. Over 51% were Medicare eligible (age ≥65 years), 53% were female, 35% had a college or postgraduate education, and 26% had estimated annual household income <$30,000. Sixty-one percent usually filled their prescriptions at retail pharmacies. Forty-one percent resided in the South geographic region and 25% in the Midwest. There were 17% of patients considered new to diabetes therapy. Patients in the study also filled prescriptions for a number of comorbid conditions: >80% filled prescriptions commonly used to treat hypertension, 67% filled prescriptions for medications to treat high cholesterol, and 25% filled prescriptions commonly used to treat chronic gastrointestinal disorders. Only 17% were treated by specialists and 4% by endocrinologists.

Patient Factors

Results of the multivariate analysis are presented in Table 2. Previous exposure to diabetes therapy had a significant impact on adherence. Patients new to therapy were 61% less likely to be adherent to their diabetes medication. There was also a clear age effect. Patients 25–44 years of age were 49% less likely to be adherent when compared with patients 45–64 years of age. Patients aged 65–74 years were 27% more likely to be adherent, and those aged 75 years and above were 41% more likely to be adherent when compared with the 45–64 year age-group. Men were significantly more likely to be adherent than women.

Table 1—Characteristics of the study population by adherence status

	Adherent		Nonadherent		Total	
Patient factors						
Total patients, *n* (%)	151,010	(69.1)	67,374	(30.9)	218,384	100%
Patient exposure to diabetes therapy, *n* (%)						
New to therapy	17,486	(11.6)	20,067	(29.8)	37,553	(17.2)
Continuing therapy	133,524	(88.4)	47,307	(70.3)	180,831	(82.8)
Patient age (years)						
Mean (SD)	66.4	(13.4)	61.6	(15.50)	64.9	(4.8)
Median	67.0		62.0		66.0	
Patient age-group (years), *n* (%)						
20–44	7,113	(4.7)	8,793	(13.0)	15,906	(7.3)
45–64	60,711	(40.2)	30,157	(44.8)	90,868	(41.6)
65–74	41,827	(27.7)	14,906	(22.1)	56,733	(26.0)
75+	41,359	(27.4)	13,518	(20.1)	54,877	(25.1)
Patient sex, *n* (%)						
Male	72,605	(48.1)	29,922	(44.4)	102,527	(47.0)
Female	78,362	(51.9)	37,430	(55.6)	115,792	(53.0)
Missing	43	(0.0)	22	(0.0)	65	(0.0)
Patient education, *n* (%)						
Completed high school	94,683	(62.7)	45,081	(66.9)	139,764	(64.0)
Completed college	39,327	(26.0)	16,052	(23.8)	55,379	(25.4)
Completed graduate school	16,237	(10.8)	5,866	(8.7)	22,103	(10.1)
Attended vocational/ technical	763	(0.5)	375	(0.6)	1,138	(0.5)
Patient income, *n* (%)						
<$30,000	41,059	(27.2)	16,566	(24.6)	57,625	(26.4)
≥$30,000 to $59,999	60,374	(40.0)	30,244	(44.9)	90,598	(41.5)
≥$60,000	49,577	(32.8)	20,584	(30.6)	70,161	(32.1)
Patient geographic region, *n* (%)						
Northeast	33,404	(22.1)	14,747	(21.9)	48,151	(22.0)
Midwest	38,080	(25.2)	15,497	(23.0)	53,577	(24.5)
West	18,263	(12.1)	8,359	(12.4)	26,622	(12.2)
South	61,263	(40.6)	28,771	(42.7)	90,034	(41.2)
Treated chronic disease conditions, *n* (%)						
Gastrointestinal	38,722	(25.3)	14,235	(22.3)	52,957	(25.1)
High cholesterol	105,336	(71.7)	36,470	(57.0)	141,806	(67.2)
Hypertension	123,563	(84.1)	47,030	(73.5)	170,593	(80.9)
Obesity	259	(0.2)	234	(0.4)	493	(0.2)
Peripheral vascular disease	4,359	(3.0)	1,640	(2.6)	5,999	(2.8)
Renal	541	(0.4)	380	(0.6)	921	(0.4)
Depression	24,826	(16.4)	10,614	(15.8)	35,440	(16.2)
Prescription factors						
Drug channel, *n* (%)						
Mail	62,957	(41.7)	22,025	(32.7)	84,982	(38.9)
Retail	88,053	(58.3)	45,359	(67.3)	133,492	(61.1)
Pill burden and cost, *n* (%)						
Total pill burden per day, mean (SD)	5.2	(3.0)	4.1	(2.5)	4.9	(2.9)
Out of pocket cost ($)/month, mean (SD)	44.68	(48.69)	69.41	(74.95)	52.31	(59.97)
Prescriber factors						
Prescriber specialty, *n* (%)						
Endocrinologist	5,494	(3.6)	2,681	(4.0)	8,175	(3.7)
Primary care	125,404	(83.0)	54,003	(80.1)	158,815	(82.2)
Other specialist	20,112	(13.3)	10,690	(15.9)	30,802	(14.1)
Prescriber age, *n* (%)						
Mean (SD)	52.9	(9.5)	52.4	(9.5)	52.7	(9.5)
Median	55.0		55.0		55.0	
Prescriber sex, *n* (%)						
Female	30,863	(20.4)	15,314	(22.7)	46,177	(21.15)
Male	120,147	(79.6)	52,060	(77.3)	172,207	(78.86)

Table 2—Odds ratios, 95% CI, and *P* values for multivariate model of factors associated with diabetes medication adherence

	Odds ratio	95% CI	*P*
Patient factors			
Patient exposure to diabetes therapy			
New to therapy vs. continuing therapy	0.39	0.38, 0.40	<0.0001
Patient age-group (years)			
25–44 vs. 45–64	0.51	0.49, 0.53	<0.0001
65–74 vs. 45–64	1.27	1.23, 1.30	<0.0001
>75 vs. 45–64	1.41	1.37, 1.44	<0.0001
Patient sex			
Male vs. female	1.14	1.12, 1.16	<0.0001
Patient education			
Vocational vs. high school equivalent	1.06	0.92, 1.22	0.4105
College grad vs. high school equivalent	1.20	1.17, 1.23	<0.0001
Graduate school vs. high school equivalent	1.41	1.36, 1.46	<0.0001
Patient income			
$30k to $60k vs. <$30k	0.93	0.91, 0.95	<0.0001
>$60k vs. <$30k	1.27	1.23, 1.30	<0.0001
Patient geographic region			
Midwest vs. West	1.12	1.08, 1.16	<0.0001
Northeast vs. West	1.04	1.00, 1.08	0.0448
South vs. West	1.00	0.97, 1.03	0.9475
Prescription factors			
Prescription drug channel: mail vs. retail	2.09	2.04, 2.13	<0.0001
Total pill burden	1.22	1.21, 1.22	<0.0001
Out-of-pocket costs (30 days)	0.89	0.89, 0.89	<0.0001
Prescriber factors			
Specialty: endocrinologist vs. primary care	1.01	0.96, 1.07	0.6076
Specialty: other specialist vs. primary care	0.91	0.89, 0.94	<0.0001
Prescriber age	1.002	1.002, 1.003	0.004

Education level and household income were both associated with adherence. The higher the estimated academic achievement, the more likely the patient was to be adherent. Patients completing graduate school were 41% more likely to be adherent when compared with patients with a high school equivalent education. Patients with an annual income >$60,000 were also more likely to be adherent when compared with patients with a household income <$30,000. There was little variation across geographic regions, although patients living in the Midwest were 12% more likely to be adherent than patients in the West.

Prescription Factors

The largest effect size was observed for patients obtaining their prescription antidiabetic medications by mail. Patients using the mail channel were more than twice as likely to be adherent to their antidiabetic medications when compared with patients filling their prescriptions at retail pharmacies. Total daily pill burden was positively associated with antidiabetic medication adherence. For each additional pill a patient took per day, adherence to antidiabetic medications increased by 22%. Patient out-of-pocket costs were negatively associated with adherence. For each additional $15 in out-of-pocket costs per month, diabetes medication adherence decreased by 11%.

Prescriber Factors

We found few meaningful differences in patient adherence according to prescriber factors. There were no differences in patient adherence by sex of the prescriber. Although there was a statistically significant association of adherence with prescriber age, the effect size was very small (for each additional year of prescriber age, the odds of adherence increased by 0.2%). There was no difference in adherence between those with primary care and endocrinologist prescribers, although the proportion of the latter was low. Patients with nonendocrinologist specialist prescribers showed slightly but significantly lower adherence than those with primary care prescribers.

CONCLUSIONS

We found that several patient demographic and clinical factors were associated with higher adherence to noninsulin antidiabetic medications: older age, male sex, higher education level, higher income, and presence of comorbid chronic conditions. Being new to diabetes therapy was associated with lower adherence. Prescription and "system" factors associated with higher odds of adherence included using a mail order channel versus retail pharmacies and having a higher total daily pill burden. Higher total out-of-pocket costs were associated with lower odds of adherence. Specialty was the only prescriber factor that was independently associated with adherence; compared with patients of primary care prescribers, patients of nonendocrinology specialist prescribers had slightly lower odds of adherence.

Prior studies on the effects of age on adherence have provided contradictory results. Older patients had higher adherence to medications for any of eight chronic conditions, including diabetes (15), and specifically for their first prescription for an oral antidiabetic medication (16). However, an analysis of adherence to guideline-based medication use for patients with cardiovascular disease found that younger patients were more likely to be adherent (17). Lower rates of medication adherence in women have been reported for statin use (18) and in studies looking at medications for a variety of chronic conditions, including diabetes (15,19).

Although polypharmacy is an important risk factor for medication interactions and adverse events, our analyses suggest that it is associated with higher, rather than lower, odds of adherence to antidiabetic medications. This association was also noted in a large study of adherence to medications for one of eight chronic conditions, including diabetes (15). However, another study examining medications for control of blood glucose, blood pressure, and cholesterol found that a higher total number of prescribed medications was not associated with adherence to diabetes and cholesterol medications and was associated with lower adherence to blood pressure medications (20).

In our study, characteristics that suggest a "healthier" patient (being younger, new to diabetes therapy, and taking few other medications) were all associated with lower odds of adherence to antidiabetic medications. This suggests that acceptance of a chronic illness diagnosis and the potential

consequences may be an important, but perhaps overlooked, determinant of medication-taking behavior.

Our findings that use of mail order channels is associated with adherence supports the results of other studies on medication adherence (21–25). A recent analysis of refill claims by Medicare Part D beneficiaries also showed increased adherence to medications for diabetes, hypertension, or high cholesterol in those using mail order channels. Use of this channel was strongly associated with past adherence (suggesting that those more likely to adhere are more likely to select mail order channels) but was still significantly associated with current adherence when controlled for past adherence (25).

Our findings regarding income and costs are important reminders that prescribers should consider the impact of medication costs on patients with diabetes. Out-of-pocket costs are an important determinant of adherence to statins (26) and a self-reported cause of underuse of medications in one in seven insured patients with diabetes (27). Lower income has previously been shown to be associated with poor adherence to diabetes medications (15) and a self-reported cause of cost-related medication underuse (27).

Most provider factors that could be assessed in the database (provider age, sex, and geographic location) were not associated with medication adherence. Patients of endocrinologist prescribers exhibited no higher odds of adherence than patients of primary care prescribers, although the proportion of patients receiving prescriptions from endocrinologists was small. Patients of nonendocrinologist specialist prescribers exhibited lower odds of adherence than patients of primary care prescribers. These results may support other groups' findings that continuity of care (28) is associated with medication adherence and health outcomes in patients with diabetes.

There are several strengths to our study. The claims database includes a very large cohort of patients from throughout the U.S. who are cared for in diverse health systems and covered by numerous types of pharmacy benefits, which may make our results more generalizable than analyses performed in closed systems. The database includes numerous variables related to patient demographics, patient comorbidities, provider demographics and specialty, and "system" factors such as prescription refill channel and out-of-pocket costs.

Our study also has several limitations. Race/ethnicity data were not available in the database used for this study. Future studies should aim to better understand potential racial and ethnic disparities in adherence and ways to ameliorate them. Because of the methodology, we were also not able to account for primary nonadherence (not filling an initial prescription for a medication), which may be an even greater problem than lack of persistence with ongoing therapy (29). Additionally, although MPR is a well-accepted measure of medication adherence, it measures only refill behavior and not actual medication taking.

As is often done in research analyses, we dichotomized adherence based on a threshold for refill behavior, whereas adherence clearly falls on a continuum. We were unable to assess adherence to insulin therapy, as there are inherent difficulties imputing adherence from medication possession ratio for insulin (insulin doses may vary from day to day, prescribed volumes are fixed, and there may be wastage due to priming of devices and expiration of the medications). Although we were able to ascertain common comorbidities from prescription claims algorithms, we were not specifically able to account for the presence of chronic complications of diabetes, which may be associated with adherence. In addition, we did not have clinical data such as hemoglobin A_{1c} results.

Because of the complexity of the analyses, we only assessed adherence in patients who were prescribed one or two noninsulin antidiabetic medications, not in those prescribed three or more. However, patients in the latter category made up $<3.5\%$ of the total cohort. We used a modified measure of adherence to account for changing classes of antidiabetic medications, presumably due to side effects or lack of efficacy, which may be common in type 2 diabetes. However, our results were not different when these patients (5% of the total cohort) were instead considered to be nonadherent. As is the case with all large database analyses, our results are hypothesis generating and cannot prove cause and effect.

Our findings should not be used to strictly define the "nonadherent" patient. Most of the factors associated with adherence had small independent effect sizes, and there is certainly no "type" of adherent, or nonadherent, patient. Rather, our results suggest that health care providers should consider many factors beyond common wisdom when addressing the issue of medication adherence. They should not assume that patients who seem uncomplicated (young, newly diagnosed with type 2 diabetes, without substantial comorbidities) are free of barriers to medication adherence. In fact, they may need more support to help them overcome barriers to adherence, one of which may be accepting the reality of having a chronic illness. Even nonmodifiable variables can increase awareness of the common issue of nonadherence and potentially drive adherence-promoting interventions. Whenever possible, providers and payers should work together to address potentially modifiable factors associated with lower likelihood of adherence, such as minimizing out-of-pocket costs and encouraging the use of mail order channels.

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had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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