Oral Antihyperglycemic Medication Nonadherence and Subsequent Hospitalization Among Individuals With Type 2 Diabetes

DENYS T. LAU, PHD[1]
DAVID P. NAU, PHD[2]

OBJECTIVE — This study examines the association between oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Using administrative claims data (2000–2001) from a managed care organization in the Midwestern U.S., this study analyzed 900 enrollees, aged 18 years and over, with type 2 diabetes who were taking oral antihyperglycemic agents both years but who did not use insulin. Nonadherence was defined as a medication possession ratio (MPR) <80%. Multivariate logistic regression analyses were performed where hospitalization in 2001 was regressed on nonadherence to the oral antihyperglycemic drug regimen in 2000, while controlling for nonadherence to drugs for hypertension and dyslipidemia and for hospitalization in 2000, age, sex, intensity of the diabetes drug regimen, and comorbidities.

RESULTS — The proportion of enrollees who were nonadherent to the antihyperglycemic drug regimen in 2001 was 28.9%, whereas 18.8 and 26.9% were nonadherent to antihypertensive and lipid-modifying drugs, respectively. The increase in the hospitalization rate for 2001 was most apparent where the antihyperglycemic MPR for 2000 dropped to <80%. Enrollees who were nonadherent to oral diabetes medications in 2000 were at higher risk of hospitalization in 2001 (odds ratio 2.53; 95% CI 1.38–4.64), whereas nonadherence to drugs for hypertension and dyslipidemia were not significantly associated with hospitalization.

CONCLUSIONS — Patients with type 2 diabetes who do not obtain at least 80% of their oral antihyperglycemic medications across 1 year are at a higher risk of hospitalization in the following year.

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The majority of adults diagnosed with diabetes use insulin and/or oral antihyperglycemic medications, in addition to diet and exercise, to achieve adequate control of their blood glucose levels. Maintaining adherence to oral antihyperglycemic medications has been one of the key strategies in achieving long-term glycemic control (1–3). However, the overall levels of nonadherence to prescribed regimens among patients with diabetes reportedly ranges from 9% to >80%, with higher rates in symptom-free patients, depending on how adherence was defined and the study population selected (4–7). A recent study (8) of managed care enrollees found that individuals with diabetes were taking an increasing number of medications for glycemic control, as well as for typical comorbidities of diabetes such as dyslipidemia and hypertension. Consequently, the drug regimen for patients with diabetes is becoming increasingly complex, and adherence may be even more challenging.

While studies have shown that nonadherent patients with other chronic conditions, particularly schizophrenia, were at greater risk of adverse long-term health consequences, including increased hospital admissions (9,10) and higher health care costs (11), the association between poor adherence to antihyperglycemic therapies and the "downstream" utilization of health care resources has not been well studied (12,13). One recent study (14) did find strong associations between decreased antihyperglycemic medication adherence and increased total health care costs among Medicare enrollees (elderly individuals aged 65 years and older) with type 2 diabetes in a health maintenance organization. However, it is not clear whether nonadherence to oral antihyperglycemic medications will lead to a higher risk of hospitalization among nonelderly individuals with diabetes. Therefore, this study aims to determine the prevalence of nonadherence to oral antihyperglycemic medications and examine the relationship of oral medication nonadherence to subsequent hospitalization for a cohort of adult enrollees, aged ≥18 years, with type 2 diabetes in a managed care health plan. The underlying conceptual framework for this work is that nonadherence to antihyperglycemic medication would lead to poor glycemic control, which in turn would result in an increased risk of hospitalization from a broad range of diabetes-related complications.

From the [1]Pfizer Research Fellowship Program, Department of Health Management and Policy, The University of Michigan School of Public Health, Ann Arbor, Michigan; and the [2]Department of Social and Administrative Sciences, The University of Michigan College of Pharmacy, Ann Arbor, Michigan.

Address correspondence and reprint requests to David P. Nau, PhD, Assistant Professor, Department of Social and Administrative Sciences, The University of Michigan College of Pharmacy, 428 Church St., Ann Arbor, Michigan 48109-1065. E-mail: dnau@umich.edu.

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Abbreviations: MCO, managed care organization; MPR, medication possession ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

The study was reviewed and approved by the institutional review board of the University of Michigan. Data were from the administrative claims of a managed care organization (MCO) in the Midwestern U.S. with ~200,000 covered lives. The commercially insured population of the MCO was used as the sampling frame. Two years of data from 2000 and 2001 were constructed from the medical and pharmacy claims of the MCO. Medical claims files contained information on the enrollee's age, sex, dates of hospitalization, and disease diagnoses as defined by codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Pharmacy claims data included fill dates and days' supply for all medications, including the target drugs for diabetes (sulfonylureas, biguanides, thiazolidinediones, meglitinides, and α-glucosidase inhibitors) and drugs for dyslipidemia and hypertension. A final analytical file was aggregated at the personal level from claims-level databases.

The final analyses were limited to 900 enrollees, aged ≥18 years, who were in the health plan for 2000 and 2001. These enrollees had a pharmacy benefit, had ICD-9-CM codes for type 2 diabetes (250.xx), and were taking oral antihyperglycemic agents in 2000, but not insulin in either year. Enrollees with fewer than two refills for oral medications during 2000 were not included in the analysis because they lacked the prescription data necessary for determining their adherence status. Patients who used insulin were excluded because the administrative claims data do not provide sufficient detail about each patient's insulin regimen to reliably estimate their adherence (e.g., we do not know if the patient is on a sliding scale for insulin).

Variables

Adherence to oral medications was defined using the medication possession ratio (MPR), a method used in prior studies (1,15,16) to quantify medication adherence. The MPR reflects the proportion of days during which the enrollee possessed a supply of medication. The denominator in the MPR is the total number of days between the first and last refill date of oral antihyperglycemic prescriptions within a year. The numerator for the MPR was calculated by summing the days' supply for all but the last filling of the oral antihyperglycemic medications. For enrollees on multiple diabetes medications, the average of the MPRs for each medication was calculated. Days when patients were in an institutionalized care setting, such as hospitals or nursing homes, were excluded from the MPR calculation. We defined "nonadherence" as an MPR <80%, a cutoff score commonly used in the literature on chronic diseases, such as diabetes and schizophrenia, to define poor adherence (17–19). The appropriateness of the 80% cutoff score was also empirically evaluated by examining the trend in hospitalization rate across several adherence strata.

Two additional variables were created to measure nonadherence to drugs for hypertension and dyslipidemia in 2000. These variables were included in the regression model because they represent treatment for the most common comorbidities for individuals with type 2 diabetes. As with the antihyperglycemic medications, an MPR <80% was used to define nonadherence. Since not all diabetic patients were receiving these drugs, a categorical variable with three levels was created for each drug category: no drug prescribed, drug prescribed but nonadherent, or drug prescribed with good adherence.

The Charlson comorbidity index was constructed based on ICD-9-CM codes. The index assigned weights to a number of major health conditions according to a validated method originally developed by Charlson et al. (20) and later modified by Romano et al. (21,22) The comorbidity index was calculated for each enrollee by summing the assigned weights for all of the person's comorbid conditions. Because the Charlson index assigns a weight of 1 to individuals with diabetes, all individuals in this study had an index score of ≥1. Within the logistic regression model, the Charlson scores were grouped into three categories based on the distribution of scores: 1, 2–3, and ≥4.

Hospitalization in 2001 was defined as an inpatient admission with a primary diagnosis code related to diabetes or cardiovascular/cerebrovascular causes (see online appendix for ICD-9 codes [available from http://care.diabetesjournals.org]). The 2001 hospitalization variable was constructed with only these diagnoses because nonadherence to antihyperglycemic drugs is most likely to affect the risk of subsequent hospitalization from these diagnoses and less with other diagnoses. Prior hospitalization was defined as an inpatient admission for any reason in the year 2000 to reflect the patient's overall health status.

A dichotomous variable was constructed to indicate whether an enrollee used monotherapy or multiple drugs simultaneously for diabetes during 2000. Combination products that were administered as a single formulation were categorized as multiple oral therapies.

Statistical analysis

Descriptive analyses of the study sample were performed with univariate analysis of frequencies and means. Change in medication adherence scores between 2000 and 2001 was statistically tested by comparing annual MPRs within individuals using the paired *t* test. Bivariate analysis with the χ^2 test was used to examine the relationship between hospitalization in 2001 and different increments of 2000 antihyperglycemic adherence scores (defined by MPR). A multivariate logistic regression analysis (23) was performed to examine the association between hospitalization in 2001 and oral antihyperglycemic medication nonadherence in 2000, while controlling for prior hospitalization in 2000, nonadherence to medications for hypertension and dyslipidemia, age, sex, oral antihyperglycemic drug intensity (single versus multiple therapies), and the Charlson comorbidity index. All data management and statistical analyses were performed using SPSS version 11.0.

RESULTS

Sample description and prevalence of medication nonadherence

Among the study sample (n = 900), slightly more than one-half were men, and the average age was 52 years (range 19–94) (Table 1). Almost 46% were on multiple oral antihyperglycemic drug therapies in 2000, and 45.0% received at least one prescription for lipid-modifying agents and 57.3% received an antihypertensive. The proportion of the enrollees considered poorly adherent to antihyperglycemic drugs (MPR <80%) was similar for both years (28.8% for 2000 vs. 28.9% for 2001). Adherence score differences within individuals between 2000 and 2001 were not statistically significant (mean score difference 0.19%; paired t = 0.30; P = 0.77). Of patients who were

Table 1—*Characteristics of study population*

Characteristics	Percentage of enrollees
n	900
Age (years)	
<45	19.7
45–54	38.5
55–64	32.9
≥65	8.9
Sex	
Male	55.2
Female	44.8
Single versus multiple oral therapy in 2000	
Multiple therapies	45.8
Single therapy	54.2
Nonadherence to medications in 2000 (MPR <80%)	
Antihyperglycemic	28.8
Antihypertensive	18.8
Lipid-modifying	26.9
Charlson comorbidity index	
1	67.1
2–3	25.3
≥4	7.6
Hospitalizations	
2000 (all cause)	11.4
2001 (diabetes/CVD)*	6.7

*CVD represents both cardiovascular and cerebrovascular events.

prescribed a drug for hypertension or dyslipidemia, 18.9% were poorly adherent to the antihypertensive regimen, whereas 26.9% were poorly adherent to lipid-modifying agents. All other descriptive data are presented in Table 1.

Medication nonadherence and subsequent hospitalization

Table 2 shows the association between hospitalization in 2001 and different increments of antihyperglycemic adherence scores in 2000 ($\chi^2 = 10.40$; $P = 0.01$). The rate of hospitalization in 2001 increased substantially from 5.2 to 10.3% when 2000 adherence scores fell below the cutoff point of 80%. The rate of hospitalization was highest at 14.8%, when 2000 adherence scores fell below 40%.

Table 3 shows the multivariate regression analysis used to determine the association between hospitalization in 2001 and oral antihyperglycemic medication nonadherence in 2000. Compared with enrollees adherent to oral antihyperglycemic medications in 2000, enrollees who were nonadherent in 2000 were much more likely to have a hospitalization in 2001 (odds ratio 2.53, 95% CI 1.38–4.64), when controlling for age, sex, nonadherence to drugs for hypertension or dyslipidemia, intensity of the antihyperglycemic medication regimen, comorbidities, and prior hospitalization in 2000. Younger age cohorts had lower chances of being hospitalized in 2001, whereas individuals with higher Charlson comorbidity scores had elevated risks of being hospitalized in 2001.

CONCLUSIONS — Oral antihyperglycemic therapies are effective methods to control glucose levels among patients with type 2 diabetes, thus lowering their risk of developing microvascular and macrovascular complications. However, the relationship between oral medication nonadherence and hospitalization is not well established for patients with diabetes. Using administrative claims data in an MCO, this study found that among adult enrollees taking oral antihyperglycemic medications, almost 30% had poor adherence in 2000 and 2001. A significant relationship was found between antihyperglycemic medication nonadherence and subsequent hospitalization, after controlling for age, sex, adherence to antihypertensive and lipid-modifying drugs, the intensity of the diabetes drug regimen, the Charlson comorbidity index, and previous hospitalization. Enrollees who were nonadherent in 2000 were 2.5 times as likely to be hospitalized in 2001 as those who were adherent in 2000.

The relationship between medication adherence and patient outcomes is becoming more evident. Several studies have demonstrated the link between adherence to diabetes medications and metabolic control (1,24–26). Most recently, Schectman et al. (1) demonstrated that for each 10% increase in adherence to oral diabetes medications, HbA_{1c} dropped by 0.16%. Thus, improvements in medication adherence may be leading to better metabolic control, which in turn may decrease the risk of complications and hospitalization. The current study also provided empirical evidence that the relationship between nonadherence to oral antihyperglycemic medications and subsequent hospitalization could be observed within 1 year. This is consistent with other studies that demonstrated the relationship of metabolic control to health care utilization within a short time period. Wagner et al. (27) showed that improvements in glycemic control resulted in cost savings within 1–2 years of the improvement. In addition, Balkrishnan et al. (14) found strong associations between decreased antihyperglycemic medication adherence and increased total health care costs in elderly individuals with type 2 diabetes.

This study used the MPR to measure adherence. Despite its limitation (28), the use of MPR scores is a common technique in research, using pharmacy claims data to quantify medication adherence (1,15,16). The MPR only indicates prescriptions filled but not medications ingested; however, the possession of medication is the required initial step for patients to actually consume the drugs.

Furthermore, this study defined nonadherence as an MPR <80%, a common cutoff score used for many medication classes (17–19,29). The definition of nonadherence as an MPR <80% was empirically supported. As noted in Table 2, the hospitalization rate increases most dramatically as the MPR drops to <80%, and then the hospitalization rate levels off at lower levels of adherence. This finding lends support to the 80% cutoff used in this study; however, further research is necessary to identify the most clinically relevant cutoff values for nonadherence based on other types of adverse health outcomes.

Table 2—*Percentage of enrollees hospitalized in 2001 across 2000 antihyperglycemic adherence score increments* ($n = 900$)

	2000 adherence scores (MPR %)*				
	100	99 to 80	79 to 60	59 to 40	<40
n	220	421	165	67	27
2001 hospitalization†	4.1	5.2	10.3	11.9	14.8

Data are percentages. *Adherence scores are defined by the MPR in percentages; †hospitalization due to diabetes or cardiovascular causes: $\chi^2 = 10.40$; $P = 0.01$.

Table 3—*Results of multivariate logistic regression analysis for prediction of hospitalization in 2001 (n = 900)**

Independent variables	Odds ratio (95% CI)
Variable of interest	
Diabetes medication nonadherence	
MPR <80% in 2000	2.53 (1.38–4.64)†
Covariates	
Age (years)	
18–44	0.27 (0.09–0.82)‡
45–54	0.53 (0.22–1.26)
55–64	0.35 (0.15–0.84)‡
≥65	1.00
Sex	
Male	0.59 (0.33–1.06)
Female	1.00
Oral antihyperglycemic medications	
Multiple-drug therapy (2000)	1.23 (0.69–2.20)
Single-drug therapy (2000)	1.00
Antihypertensive use pattern	
None prescribed	1.00
Prescribed (nonadherent)	0.66 (0.25–1.71)
Prescribed (adherent)	0.68 (0.35–1.32)
Lipid-modifier use pattern	
None prescribed	1.00
Prescribed (nonadherent)	0.78 (0.30–2.01)
Prescribed (adherent)	1.54 (0.79–3.03)
Charlson comorbidity index	
1	1.00
2–3	4.04 (2.54–6.86)†
≥4	16.86 (7.69–36.98)†
Prior hospitalization (2000)	
Yes	1.27 (0.61–2.67)
No	1.00

*Hospitalizations are limited to those with a primary diagnosis of diabetes or cardiovascular disease; †$P \leq 0.01$; ‡$P \leq 0.05$.

Diabetes may have very broad effects on health. Poor glycemic control in type 2 diabetes produces physiological changes that result in macrovascular and microvascular complications. As shown in epidemiologic studies (30–32), many individuals with diabetes die or are hospitalized due to cardiovascular or cerebrovascular events. The hospitalization rate in this study reflected only inpatient admissions that had a primary diagnosis of diabetes or cardiovascular/cerebrovascular conditions. However, the overall rate of hospitalization (11%) is similar to that noted by Menzin et al. (33) (~10%) and Wagner et al. (27) (~15%) when using similar methods. Furthermore, the analysis used in the current study controlled for use of antihypertensive and lipid-modifying drugs, as well as for several measures of health status, including the Charlson comorbidity index, which incorporates cardiovascular conditions, and a history of prior hospitalization in the multivariate regression model. A significant association is still observed between antihyperglycemic medication nonadherence and subsequent hospitalization.

The association of medication nonadherence and poor clinical outcomes has been demonstrated in numerous populations. However, the strength of the association between antihyperglycemic therapy and hospitalization may vary based on the specific diabetic population studied. This study focused on adults, aged ≥18 years, in a managed care setting for 2 years. Even though data on socioeconomic status were not available, this study has restricted its analysis to enrollees with pharmacy benefits from the same source of health insurance and excluded those with Medicaid coverage. Furthermore, enrollees on insulin were excluded from the analysis, because it increased the certainty that the study sample had type 2 diabetes and because adherence to insulin could not be reliably estimated using administrative claims. These restrictions on the sample may have excluded patients with the worst health status, and thus the findings related to hospitalizations may be conservative.

In summary, patients with type 2 diabetes who fail to obtain at least 80% of their antihyperglycemic medications across a 1-year time frame are at a significantly higher risk of hospitalization during the following year. If strategies can be developed to identify and intervene with these patients, there may be substantial benefits to patients as well as the payers for health care services.

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