Relationship of Oral Antihyperglycemic (Sulfonylurea or Metformin) Medication Adherence and Hemoglobin A1c Goal Attainment for HMO Patients Enrolled in a Diabetes Disease Management Program

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ABSTRACT

BACKGROUND: There is limited information in the primary literature regarding the relationship of medication adherence to attainment of glycosylated hemoglobin A1c (A1c) goals. The 2 oral antihyperglycemic medications, sulfonylurea and/or metformin, were chosen for retrospective analysis because they are the 2 most common oral medications used by patients with diabetes.

OBJECTIVE: To describe the relationship between adherence with 1 or both of 2 oral antihyperglycemic medications (sulfonylurea and metformin) and A1c goal attainment for health maintenance organization (HMO) patients enrolled in a diabetes disease management program.

METHODS: This was a retrospective, descriptive evaluation of patients enrolled in a managed care diabetes disease management program in a 188,000-member independent practice association model HMO located in the Southeast. The dataset in this analysis contained demographic, enrollment, pharmacy claims, and clinical laboratory data. Continuously enrolled patients were included if there was a documented A1c value obtained at least 90 days after the initial oral antihyperglycemic medication (sulfonylurea or metformin) prescription index date. The medication possession ratio (MPR) was calculated from the pharmacy claim records and correlated with the A1c value.

RESULTS: A total of 42% of patients on sulfonylurea therapy and 46% of those on metformin reached an A1c goal of $\leq 7.0\%$. For patients taking a sulfonylurea, the mean MPR for those who reached the predetermined A1c goal (≤ 7.0) was 0.82 (± 0.29) compared with 0.72 (± 0.31) for those patients who did not reach the A1c target goal ($P < 0.001$). For patients taking metformin, the mean MPR for those who reached the predetermined A1c goal was 0.77 (± 0.3) versus 0.62 (± 0.3) for those patients who did not reach the A1c target goal ($P < 0.001$). A Pearson correlation analysis revealed a positive relationship between the MPR and A1c for sulfonylurea ($r = -0.295$, $P < 0.001$) and for metformin ($r = -0.285$, $P < 0.001$). For those patients taking both sulfonylurea and metformin, the Pearson correlation analysis showed a positive relationship between the 2 MPRs ($r = 0.65$, $P < 0.001$).

CONCLUSION: Medication adherence as measured by the MPR was higher for patients taking a sulfonylurea or metformin who reached the target A1c goal of $\leq 7.0\%$ compared with patients taking these drugs who did not reach the target A1c goal.

KEYWORDS: Adherence, Diabetes, Disease management, Managed care, Sulfonylurea, Metformin, Medication possession ratio, Hemoglobin A1c

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In the United States, approximately 7% of the population has diabetes, which ranks as the sixth leading cause of death, with corresponding annual costs of more than \$130 billion.¹ Clinical trials have demonstrated that tight glycemic control (A1c [glycosylated hemoglobin] $< 7\%$) is associated with a significant reduction in microvascular complications as well as a trend toward reduction of macrovascular complications.²⁻⁴ In light of this information and at the time that this study was conducted, the American Diabetes Association (ADA) recommended that the target for long-term glycemic control in patients with diabetes is an A1c value of less than 7%.⁵

Obviously, there are many factors that contribute to successful blood glucose control, including appropriate diet, exercise goals, and patient motivation. Oral medications also play an important role in the management of type 2 diabetes. With evidence linking such pharmacological modalities to better outcomes, awareness of the critical role of adherence to pharmacologic therapy has been heightened. A recent meta-analysis showed that the average adherence to therapy in patients with diabetes is 67.5%, which is lower than that seen with various other conditions such as human immunodeficiency virus disease, osteoarthritis, gastrointestinal disorders, and cancer.⁶ In addition, a systematic review of adherence to medications for diabetes showed that average adherence to oral antihyperglycemic medications ranged from 36% to 93% for patients who remained on treatment for 6 to 24 months.⁷

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Poor medication adherence would seem to be a significant barrier to attainment of positive clinical outcomes such as a decrease in both micro- and macrovascular disease. Although there are studies in the literature regarding clinical and intermediate outcomes,⁸⁻¹⁰ there is a continuing need to measure the relationship between medication adherence and intermediate outcomes such as A1c and long-term clinical end points. Analyses of administrative claims that include laboratory values can inform about the relationship between medication adherence and intermediate clinical outcomes.

The purpose of this retrospective, descriptive evaluation was to determine the adherence rates for 2 commonly used oral antihyperglycemic medications in a diabetic patient population and the relationship of adherence to A1c target goal attainment. Our hypothesis was that there is a direct relationship between medication adherence and attainment of the target goal A1c of $\leq 7\%$.

Methods

This study used information from the approximately 6,000 patients already participating in the diabetes disease management program (begun in 1994) of a 188,000-member independent practice association model health maintenance organization (HMO) in South Carolina. Type 1 and Type 2 diabetes patients were included in the disease management program when pharmacy and/or medical claim records indicated a diabetes diagnosis (ICD-9 [International Classification of Diseases, Ninth Revision] codes 250, 357.2, 362, 366.41). Patients were also identified through laboratory data (A1c tests) or physician or patient self-referral. Components of the diabetes management program included counseling by the plan's certified diabetes educator, written diabetes education material, written and verbal encouragement for scheduled visits to physicians, and monitoring of quality measures.

At the time of this study, medication adherence counseling was not part of the program. Nearly all prescriptions for these patients were filled through community pharmacies, and use of mail-order pharmacy service by these patients was minimal. It is estimated that approximately 50% of the patients in the program had their pharmacy benefit managed by this HMO, with the other 50% administered through a contract with a carve-out pharmacy benefit management relationship. Only the patients with the HMO-managed benefit were included in this analysis.

The focus of the present study was the use of oral anti-hyperglycemic agents, defined as all available sulfonylureas, metformin, and combination products containing either of these ingredients. At the time of this evaluation, the use of thiazolidinediones, alpha glucuronidase inhibitors, and meglitinide was becoming increasingly common. However, we chose to focus on the 2 most commonly used drugs, which had at least 9 months of claims data required for the adherence

TABLE 1A Sample Selection for Sulfonylurea Patients

Criteria	Target Medication	Number of Patients Remaining (%)	Number of Patients Dropped (%)
Patients in diabetes disease management program and with drug benefit claims and continuous plan enrollment January 1, 2001, through December 31, 2002	All medications	2,995 (100)	0 (0)
Patients with at least 1 claim for target oral antihyperglycemic medication (sulfonylurea)	Sulfonylurea	1,370 (45.7)	1,625 (54.3)
First date of target medication before March 31, 2002	Sulfonylurea	894 (29.8)	476 (15.9)
Patients with A1c lab date ≥ 90 days after first date of target medication	Sulfonylurea	655 (21.9)	239 (7.9)

A1c = glycosylated hemoglobin.

TABLE 1B Sample Selection for Metformin Patients

Criteria	Target Medication	Number of Patients Remaining (%)	Number of Patients Dropped (%)
Patients in diabetes disease management program and with drug benefit claims and continuous plan enrollment January 1, 2001, through December 31, 2002	All medications	2,995 (100)	0 (0)
Patients with at least 1 claim for target oral antihyperglycemic medication (metformin)	Metformin	1,533 (51.2)	1,462 (48.8)
First date of target medication before March 31, 2002	Metformin	1,065 (35.6)	468 (15.6)
Patients with A1c lab date ≥ 90 days after first date of target medication	Metformin	1,013 (33.8)	52 (1.7)

A1c = glycosylated hemoglobin.

calculation. Insulin was not evaluated because of the challenge of calculating adherence from multiple-dose vials.

The target oral antihyperglycemic agents were identified from the pharmacy claims database for the 2 years between January 1, 2001, and December 31, 2002. Patients would be included if they were continuously enrolled over this time period and had 1 pharmacy claim for the target agent. Pharmacy records were used to compute a 9-month, cumulative medication possession ratio (MPR), defined as the ratio of the total days supply of medication that was dispensed divided by the number of days in the evaluation period (270 days). An MPR of greater than 1.0 was included in analysis. The MPR could be greater than 1.0 if, for example, patients obtained the medication early or if they switched to a different product containing the

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TABLE 2 Patient Characteristics and Key Findings

Characteristic	Metformin	Sulfonylurea
No. of patients	1,013	655
% male	41	48
Mean age [SD]	51.0 [±8.9]	52.2 [±8.5]
Mean MPR [SD]	0.69 [±0.34]	0.76 [±0.31]
Mean A1c [SD]	7.8 [±2.1]	7.9 [±2.0]
% and (no.) at A1c goal ≤7%	46 (470)	42 (272)
% and (no.) with insulin claims	22 (223)	18 (118)
% and (no.) on both metformin and sulfonylurea	40 (402)	61 (402)
% and (no.) on other oral antihyperglycemic*	45 (460)	48 (315)
Average [SD] days supply for study drug (9 months)	188.2 [±91.4]	207.5 [±84.0]
Average [SD] days supply per Rx	33.1 [14.6]	33.0 [14.3]

* Thiazolidinediones, alpha glucuronidase inhibitors, or meglitinides.
A1c=glycosylated hemoglobin; MPR=medication possession ratio;
Rx=prescription.

FIGURE 1 Mean MPR (With 95% Confidence Interval Bars) of Patients Reaching and Not Reaching A1c Goal (≤7.0%)

A1c=glycosylated hemoglobin; MPR=medication possession ratio.

target medication before using all the available medication. Adherence calculations were performed using the Standardized Therapy Adherence Research Tool (START; Pfizer, Inc.) software.¹¹ All A1c measurements available for these patients over the same period were identified. A1c goal was defined as ≤7.0%, which differs from the target of <7.0% specified by the ADA.¹²

The most recent A1c value was the single value used for analysis. Patients were excluded if (1) they did not have at least 1 A1c laboratory value, (2) if the most recent A1c measurement was less than 90 days after the first oral antihyperglycemic claim (i.e., the A1c is a reflection of blood glucose control over the prior 90 days, and this minimum amount of time was required

after the initiation of the oral antihyperglycemic agent), and (3) if their first pharmacy claim for the target oral antihyperglycemic agent was after March 31, 2002 (in order to have a complete 9 months available for calculation of the MPR).

MPR and A1c goal analyses were performed for the each of the target drugs, metformin and sulfonylurea, without regard to other antihyperglycemic agents being taken, including insulin. MPR ranges were used to describe the average A1c and percentage of patients reaching A1c goal. Patients taking both targeted classes were included in the combined analysis and in the individual class analysis. Mean MPR was compared for patients reaching and not reaching the A1c goal, using Student's *t* test (comparing the MPRs [cumulative] of patients reaching goal versus those not reaching A1c goal) and the Pearson correlation coefficient to describe the MPR and A1c relationship for the population. A subanalysis of patients on both sulfonylurea and metformin was performed to describe the medication-taking relationship in this population and was evaluated statistically, using the Pearson correlation analysis. Ninety-five percent confidence intervals were used to evaluate results. A *P* value <0.05 was required for statistical significance in all analyses.

Results

There were a total of 2,995 diabetic patients identified with pharmacy claims. With regard to sulfonylurea agents, 655 patients met the inclusion-exclusion criteria for final analysis. (Table 1A) Forty-eight percent of patients were male; the average age was 52.2 (±8.5) years and the average A1c was 7.9% (±2.0). Of these patients, 272 (42%) reached an A1c goal of ≤7.0% (Table 2). The average MPR for this group was statistically higher than the mean MPR of those not reaching goal (0.82, compared with 0.72; *P* <0.05) (Figure 1). A Pearson correlation analysis showed a significant, inverse association between A1c and MPR (*r* = -0.295, *P* <0.001). In general, the data showed that when the MPR increases, A1c values decrease (Figure 2).

With regard to metformin, 1,013 patients met the inclusion-exclusion criteria for final analysis (Table 1B). Forty-one percent of patients were male; the average age was 51.0 (±8.9) years and the average A1c was 7.8% (±2.1). Of these patients, 470 (46%) reached an A1c goal of ≤7.0%. The mean MPR for this group was statistically higher than the mean MPR of those not reaching goal (0.77, compared with 0.62; *P* <0.05) (Figure 1). A Pearson correlation showed a significant, inverse association between A1c and MPR (*r* = -0.285, *P* <0.001). Again, the data showed that when the MPR increases, A1c values decrease (Figure 3).

A total of 402 (13%) patients (13%) were taking both a sulfonylurea and metformin, and a correlation analysis was performed to determine the MPR relationship between these classes of antihyperglycemic medications. A Pearson correlation did demonstrate a significant, positive association between

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sulfonylurea and metformin MPRs ($r=0.65$, $P<0.001$) (Figure 4). Although the impact of insulin use was not part of our original investigation, patients who were taking insulin with a sulfonylurea and/or metformin (18% and 22% of patients, respectively) had a mean MPR of $0.65 (\pm 0.35)$; 0.57 ± 0.34 .

Discussion

Our evaluation demonstrated that oral antihyperglycemic-medication-taking behavior as measured by the medication possession ratio is related to A1c goal attainment in patients with diabetes. We evaluated both type 1 and type 2 diabetes patients enrolled in a managed care diabetes disease management program and specifically evaluated adherence to 2 common oral antihyperglycemic medications, separately and when used in combined therapy. Some previously published reports stand in contrast to our findings, finding no relationship between medication adherence and A1c goal attainment. However, these studies relied upon self-reported adherence only, and the validity of this measure might be questioned.¹³⁻¹⁶

There are published reports that do demonstrate an association between adherence to medication regimens and improved glycemic control, similar to our study. For example, Pladevall et al.⁸ evaluated 677 patients aged 18 years or older with a diagnosis of diabetes, hypercholesterolemia, and hypertension and who filled at least 1 prescription for either an antihyperglycemic, lipid-lowering, or antihypertensive drug in each of 3 study years. Main outcome measures included A1c, low-density lipoprotein cholesterol, and blood pressure. It was shown that, after adjustment for demographic and clinical characteristics, nonadherent patients had both statistically and clinically worse outcomes than adherent patients. Specifically, a 10% increase in nonadherence to metformin was associated with an increase of 0.14% in A1c ($P<0.01$).

Krapek et al.⁹ assessed adherence in 301 patients with type 2 diabetes using the Morisky survey (a 4-item questionnaire that predicts patient medication-taking behavior—a higher score on the scale of 0 to 4 indicates better adherence to treatment). Mean A1c values for patients with Morisky scores of 0 or 1, 2, 3, and 4 were 8.92%, 8.67%, 7.74%, and 7.60%, respectively. A Morisky score of greater than or equal to 3, indicating good adherence, was associated with a 10% lower total A1c ($P<0.001$).

Schectman et al.¹⁰ used a claims database to correlate A1c values with drug adherence. The study population consisted of 810 patients with type 2 diabetes who were currently taking oral antihyperglycemic medications and had at least 1 A1c value obtained during the study period. Improved metabolic control was independently associated with greater medication adherence. For each 10% increase in drug adherence, A1c decreased by 0.16% ($P<0.001$). These 3 trials demonstrate similar findings to our study, in that higher medication adherence appears to be correlated to lower A1c values.

Other older, smaller studies using objective adherence measures

FIGURE 2 Sulfonylurea MPR Range and A1c (Average)

A1c=glycosylated hemoglobin; MPR=medication possession ratio.

FIGURE 3 Metformin MPR Range and A1c (Average)

A1c=glycosylated hemoglobin; MPR=medication possession ratio.

FIGURE 4 Correlation Analysis of Metformin MPR and Sulfonylurea MPR for Patients on This Dual Therapy

MPR=medication possession ratio.

have also demonstrated associations with diabetes control.¹⁷⁻²⁰ These older studies used pill counts to assess adherence and A1c values to determine diabetes control.

In addition to A1c values, which our study focused on, non-adherence to oral antihyperglycemic medications may also lead to negative patient-oriented outcomes as well as economic implications. Lau and Nau used administrative claims data from a managed care organization in order to evaluate patients with type 2 diabetes who were currently taking oral antihyperglycemic medications.²¹ Nonadherence was defined as an MPR <80%. Patients who did not obtain at least 80% of their oral antihyperglycemic medications over a 1-year period were at a higher risk of hospitalization in the following year (odds ratio 2.53; 95% confidence interval, 1.38-4.64). Sokol et al.²² conducted a retrospective cohort observation of approximately 137,000 patients who were enrolled in medical and prescription benefit plans. Medication adherence was defined as the percentage of days during the analysis period that patients had a supply of one or more maintenance medications for the condition (based on “days’ supply” data in patients’ prescription claim records). For patients with diabetes, a high level of medication adherence (>80%) was associated with lower disease-related medical costs. These differences were statistically significant ($P < 0.05$). Patients who maintained 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence ($P < 0.05$).

Hepke et al.²³ used a retrospective cohort design to evaluate insurance claims in an open access, nonmanaged care setting. In this evaluation, increased medication adherence was associated with fewer emergency room visits, hospitalizations, and decreased medical care costs. For those patients with diabetes as their primary diagnosis, the threshold of 40% to 59% adherence was associated with a subsequent decrease in medical care cost and use of health care resources other than pharmacy. Balkrishnan et al.²⁴ also examined the relationship between oral antihyperglycemic medication adherence and health care service utilization in 775 older adults with type 2 diabetes in a managed care setting. After controlling for the type of pharmacologic therapy as well as other variables, increased MPR was the strongest predictor of decreased total annual health care costs (8.6% to 28.9% decrease with every 10% increase in MPR; $P < 0.001$). Adherence to oral antihyperglycemic medications was associated with a greater cost reduction than other medications in this population, including antihyperlipidemic agents.

Limitations

Foremost among the study limitations was the choice of the cut-off for A1c values, resulting in categories that do not match precisely the guidelines of the American Diabetes Association. We defined A1c values of $\leq 7.0\%$ as goal, while the ADA recommends a goal of $< 7.0\%$. Therefore, our target A1c value is slightly

less stringent than the ADA guideline and much less stringent than the A1c target of $\leq 6.5\%$ recommended by the American Association of Clinical Endocrinology.²⁵

Second, the present study could not establish a clear temporal relationship between drug use and the A1c value recorded in the database. Since only 1 pharmacy claim was required for inclusion in the study, it is possible that a patient received as little as 30 days of the study drug, and the A1c value might have been recorded after 90 days from the date of the first and only pharmacy claim for the study drug. However, the average days supply and standard deviation (SD) over 9 months for the study drugs were 188.2 days (91.4 SD) for metformin patients and 207.5 days (84.0 SD) for the sulfonylurea patients. This potential limitation is offset, however, by the manner in which we defined MPR, the total days of therapy dispensed to each patient divided by 270 days. This method of MPR calculation—a cumulative MPR²⁶—will tend to result in a lower average MPR, typically calculated by the days supply divided by the difference between the first and last fill dates. We did, however, include (cumulative) MPR values greater than 1.0, whereas other researchers may reduce MPR values greater than 1.0 to 1.0 since the practical maximum value is 100% medication possession during the observation period.

Third, this is a study of an intermediate therapeutic outcome (i.e., laboratory A1c value), not end point clinical outcomes such as hospitalizations or emergency room visits.

Fourth, we did not assess severity of illness in these patients.

Fifth, we did not determine potential cost savings in this patient population. Other studies have done so (as above) with positive results.²²⁻²⁴ Our results also suggested that insulin utilization seemed to be a negative factor in relationship to oral antihyperglycemic medication MPR (patients who were taking insulin with a sulfonylurea and/or metformin [18% and 22% of patients, respectively] had a mean MPR of 0.65 (± 0.35); 0.57 $\pm$ 0.34). In other words, those patients using insulin had lower rates of adherence to their oral medications. These data were not a part of the original hypothesis; however, this finding does deserve further analysis, with a focus on the timing of the insulin initiation and the pre-MPR and post-MPR of the oral antihyperglycemic medication. It could be hypothesized that the addition of insulin may be a result of poor oral antihyperglycemic adherence in and of itself.

Given the need for these patients to take a variety of medications, with different dosage frequencies and numbers of tablets at various times of the day, it is not surprising that nonadherence occurs.^{27,28} As would be expected, there seems to be a negative impact of complex treatment regimens on routine adherence to drug therapy. On the other hand, the more information and understanding that patients have regarding their disease states and pharmacologic therapies, the more likely they are to adhere to those therapies.²⁹

Our study adds to the limited amount of information to the

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literature, as above, especially with regard to data retrieved from a claims database. In addition, our study included both type 1 and type 2 diabetes patients, looked at 2 specific oral antihyperglycemic medications, and evaluated these medications both separately and together. Although we did not evaluate the correlation between improved adherence and patient-oriented/economic outcomes, results of previous studies would suggest that improved adherence and subsequently lower A1c values does indeed lead to decreased hospitalizations, emergency room visits, and overall health care costs.

Conclusion

Our evaluation demonstrated that oral antihyperglycemic medication adherence with sulfonylurea or metformin is associated A1c goal attainment. The use of adherence measurement should be considered by health plans in their population management strategies. Nonadherence to medications should be considered by health care providers when patients do not reach target A1c goal.

DISCLOSURES

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