

Oral Antidiabetic Medication Adherence and Glycemic Control in Managed Care

Yelena Rozenfeld, MPH; Jacquelyn S. Hunt, PharmD,
Craig Plauschinat, PharmD, MPH; and Ken S. Wong, PharmD

Type 2 diabetes is a growing worldwide epidemic, with approximately 20 million diagnosed and undiagnosed persons in the United States.¹ Of national concern is the finding that fewer than half of Americans with diabetes have achieved a glycosylated hemoglobin (A1C) level of <7%.² Nonadherence to medication therapy is among several factors contributing to suboptimal glycemic control. A recent systematic review found significant variation in adherence to oral diabetes medications (ODMs), ranging from 36% to 93%.³ Patient nonadherence to medications prescribed for diabetes has been shown to decrease treatment effectiveness⁴⁻⁶ and increase healthcare costs.^{7,8} Although published studies address clinical outcomes, there is a continuing need to evaluate the association between medication adherence and diabetes outcomes. The purposes of this study were to evaluate (1) patient adherence to ODM and (2) the relationship between adherence and glycemic control.

METHODS

Setting and Study Population

This retrospective cohort study was conducted by the Providence Primary Care Research Network in Oregon within an integrated delivery network. After institutional review board approval, medical and pharmacy claims were received from the network managed care plan with a 2-tier pharmacy benefit design. Eligible patients were identified based on the following criteria: age ≥18 years, a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision* code 250.xx), an ODM prescription (January 31, 2001, through December 31, 2004), and continuous enrollment for 6 months or more. Patients were followed for 12 months from the date of the first ODM prescription fill (the index date). Patients were required to be ODM therapy naive (no fills for any ODM during the 6 months before the index date). ODM agents were grouped by therapeutic class, including metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), α -glucosidase inhibitors, and meglitinides. Patients whose index diabetes medication was insulin were excluded. Because of small sample size, study results are not presented for patients whose index regimen consisted of an α -glucosidase inhibitor or a meglitinide.

Objective: To evaluate adherence to oral diabetes medications (ODMs) in patients with type 2 diabetes and the impact of ODM adherence on glycemic control.

Study Design: Retrospective observational study.

Methods: Medical and pharmacy claims from a managed care plan in Oregon were used to identify adults with diabetes who newly initiated ODM therapy (n = 2741); a subset of this cohort linked to electronic health records was used to evaluate the relationship between adherence and glycemic control (n = 249). Glycemic control was assessed based on most recent glycosylated hemoglobin (A1C) measurement within the study period.

Results: Mean cohort age was 54 years; 46% initiated therapy with metformin, 39% with a sulfonylurea, and 12% with a thiazolidinedione. Mean adherence overall was 81%, and 65% of subjects had good adherence (≥80%). Increasing age and comorbidity burden were associated with higher medication adherence. In the patient subset with A1C measurements, mean baseline A1C was 8%. An inverse relationship existed between ODM adherence and A1C; controlling for baseline A1C and therapy regimen, each 10% increase in ODM adherence was associated with a 0.1% A1C decrease (P = .0004).

Conclusion: Although most patients were adherent to ODM therapy, adherent patients were more likely to achieve glycemic control than nonadherent patients. Greater efforts are needed to facilitate diabetes self-management behaviors to improve patient outcomes.

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Variable Definitions

Medication adherence was calculated for all patients with at least 2 fills of the

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■ CLINICAL ■

index ODM, and was defined as the sum of the days supply from the index prescription date to the last fill date (excluding days supply that was dispensed at the final prescription fill), divided by the duration of therapy. Patients using free combinations of more than 1 ODM were classified according to the first medication that was filled during the study period, and study metrics were calculated for that drug. For free combination regimens, patients were considered adherent on a specific day if all drugs were considered to be “on hand” on that date. Patients with adherence of less than 80% were classified as nonadherent.

Patients’ complete refill history at baseline was used to calculate the modified chronic disease score (CDS) to assess patient comorbidity.⁹ The number of concurrent (non–diabetes-related) medications also was assessed as another measure of disease burden.

A subset of study patients who also received care from primary care physicians employed within the integrated delivery network was identified to evaluate the relationship between medication use and glycemic control. This subset was limited to patients with an A1C test result at study baseline (180 days before the study index date and 60 days subsequent to the index date). Glycemic control at follow-up was assessed after a stabilization period subsequent to ODM initiation; it was based on the most recent A1C within the study period, collected at least 60 days after the index date.

Statistical Analysis

Descriptive statistics were produced for appropriate variables. Continuous data were described by means and standard deviations, and nominal and categorical data were described by frequencies and percentages. Unadjusted

demographic, clinical, and medication characteristic comparisons between groups were completed by using *t* tests, analysis of variance, and correlation analysis for evaluation of continuous variables and the χ^2 test for categorical variables.

Multiple regression was used to evaluate the relationship between adherence and glycemic control by means of a backward elimination process. Several patient-related and provider-related factors were used as covariates in the model for statistical adjustment, including original ODM regimen, baseline A1C, sex, age at index date, CDS, and medication burden, as well as provider sex, specialty, and years since medical school graduation. All variables except baseline A1C and index ODM regimen were eliminated as nonsignificant predictors. The index regimen was categorized as following: (1) metformin, (2) metformin + SU, and (3) SU. All data manipulation and statistical analysis were completed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The cohort of patients who newly initiated ODM therapy included 2741 subjects for evaluation of utilization metrics. Mean cohort age was 54 ± 11 years, and 49% were female (Table). Overall, 84% initiated ODM monotherapy, 15% initiated dual combination therapy, and 1% initiated triple combination therapy; 41% were prescribed metformin, 33% SUs, 9% TZDs, 2% other drugs (including α -glucosidase inhibitors and meglitinides), and 15% were prescribed various combination therapies. The mean CDS overall was 2.89 ± 0.99 , with a small but significant difference between SU and TZD patients (2.85 vs 2.99 , $P = .04$).

■ **Table.** Patient Cohort Demographic Characteristics and Drug Utilization Metrics by Index Drug Class*

Characteristic	Metformin (n = 1274)	Sulfonylureas (n = 1081)	Thiazolidinediones (n = 337)	Total [†] (n = 2741)
Age, y	53 ± 11	55 ± 12	52 ± 11	54 ± 11
Female, %	54	49	51	49
CDS	2.89 ± 0.96	2.85 ± 1.0	2.99 ± 0.97	2.89 ± 0.99
Patients with >1 fill of index drug, n (%)	1001 (78.6)	861 (79.6)	264 (78.3)	2126 (77.6)
Adherence, % [‡]	80.7 ± 21.6	81.8 ± 21.7	82.0 ± 21.4	81.3 ± 21.6
Adherence ≥80%	63.9%	65.8%	69.4%	65.4%

*Data are given as mean ± SD unless otherwise indicated.

[†]Because of small sample size, results for patients whose index drug was an α -glucosidase inhibitor or a meglitinide (n = 49) are not presented by index drug category in the Table, although they are included in the “Total” column.

[‡]Adherence was calculated for the patient subset with at least 2 fills of the index drug(s).

CDS indicates chronic disease score.

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Mean adherence for the study cohort was 81% and did not significantly differ by therapeutic class. The effect of patient clinical and demographic characteristics on index ODM adherence was evaluated. Older patients were more likely to be adherent (mean age 56 years vs 52 years, $P < .0001$), but there was no difference between men and women in adherence ($P = .61$). Adherent patients had a significantly higher disease burden, as measured by either CDS (2.99 vs 2.86, $P = .0022$) or total medication burden (10.3 vs 9.6, $P = .022$), than patients classified as nonadherent.

In the patient subset with A1C test results ($n = 249$), mean baseline A1C was $8.0\% \pm 1.5\%$. Approximately 44% of this subset initiated ODM therapy with metformin, 38% with SUs, and 12% with combination (metformin plus SU) therapy. Additionally, these patients were not different from the main study population with respect to age, sex, and CDS.

For patients initiating index ODM therapy with SU, metformin, or metformin plus SU ($n = 235$; TZD patients were excluded because of small sample size), multiple regression was used to determine the relationship between adherence and A1C, controlling for therapeutic regimen and baseline A1C. An inverse relationship was observed between ODM adherence and A1C (Figure), in which a 10% increase in index ODM adherence was associated with a 0.1% decrease in A1C ($P = .0004$). Index ODM regimen also was significantly associated with A1C; metformin demonstrated a stronger association ($P = .02$) than SU ($P = .04$).

DISCUSSION

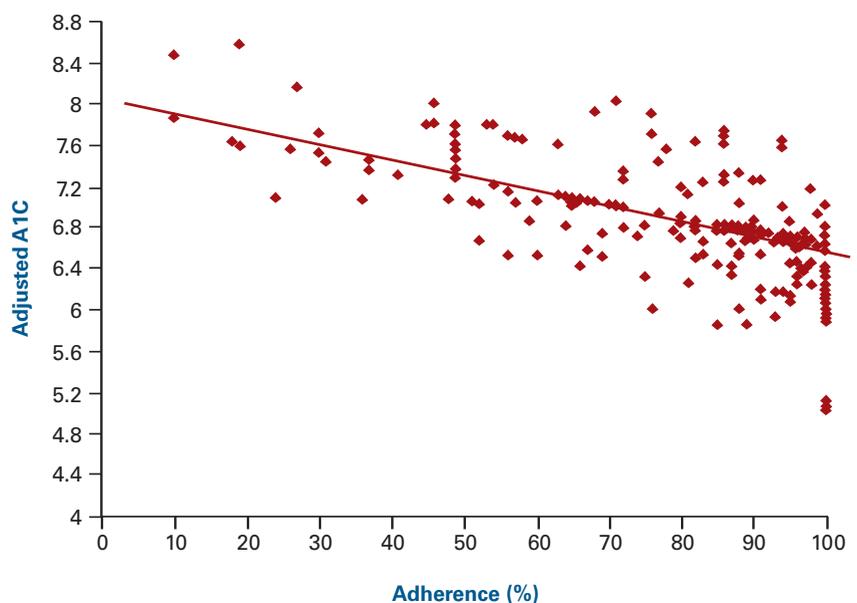
This study in a managed care setting found that 65% of patients with diabetes had good adherence with initial ODM. In the subset with A1C results, baseline mean A1C was 8%, and 61% of all patients subsequently achieved glycemic control. Adherence was higher among patients achieving glycemic control, and an inverse relationship was found between ODM adherence and A1C. Controlling for baseline A1C and therapy regimen, each 10% increase in ODM adherence was associated with a 0.1% A1C decrease.

This study found a mean adherence rate of 81%. A recent review of studies evaluating adherence found a range of 36% to 93% for antidiabetic

medications.³ However, these findings should be interpreted cautiously, as the studies included diverse populations, various methods for calculating adherence, and different study durations. Many of these studies also included adherence to insulin, which is difficult to estimate based on methodology that relies on pharmacy claims. Other investigators have found adherence rates similar to ours at 1 or 2 years subsequent to new ODM initiation in managed care settings.^{10,11} Using a claims database from a national pharmacy benefits manager, one of the largest studies found mean 1-year adherence was 79% in a cohort of 79 498 new ODM users.¹¹ As in our study, these researchers found similar rates of adherence among patients taking metformin and those taking SUs, and they did not include currently marketed TZDs because of insufficient data. Other similar ODM studies conducted outside the United States also have demonstrated consistent results.¹²⁻¹⁴

Our finding of an association between increasing comorbidity and adherence needs to be interpreted with caution because this association is not reported consistently in the published literature. Although some studies reported no association or negative association,^{15,16} several publications reported results similar to those in our study.^{17,18} Furthermore, it is conceivable that patients with a higher number of chronic conditions are better informed about diabetes and its complications and, therefore, would maintain greater rates of

■ **Figure.** Association Between A1C and Adherence, Adjusted for Baseline A1C and the ODM Regimen*



*Metformin plus a sulfonylurea was used as the reference group for the index ODM regimen. A1C indicates glycosylated hemoglobin; ODM, oral diabetes medication.

Take-away Points

In a managed care setting, this retrospective study demonstrated that although most patients were adherent with prescribed oral diabetes medication (ODM), about 35% of patients were classified as nonadherent.

- After adjusting for baseline glycosylated hemoglobin (A1C) and therapy regimen, each 10% increase in adherence with ODM was associated with a 0.1% A1C decrease.
- When lab data are not available (as is common in managed care databases), pharmacy claims may serve to identify patients for targeted outcomes/intervention programs.
- Greater efforts are needed to improve medication adherence and patient self-management in type 2 diabetes.

adherence despite their greater medication burden and numerous comorbidities.

Several studies of the impact of adherence on glycemic control have been conducted, primarily using cohorts derived from managed care databases with limited geographic representation. One study of 677 patients from Michigan diagnosed with diabetes, hypercholesterolemia, and hypertension found a 10% increase in nonadherence to metformin and statins related to a 0.14% increase in A1C.¹⁹ Schectman et al studied 810 patients with type 2 diabetes from a clinic serving a low-income population in central Virginia and found that for each 10% increase in adherence, A1C decreased by 0.16%.⁵ Another cross-sectional study of 301 patients from 6 regional practice sites, which used the patient questionnaire-based Morisky score to evaluate adherence, found that better adherence was associated with a 10% lower A1C, adjusted for covariates.⁶ Finally, a study of 2995 patients from a managed care organization in the southeastern United States who were prescribed metformin or SU found significantly higher mean adherence for patients who reached the goal A1C of $\leq 7\%$ (77% and 82%, respectively) than for patients who did not (62% and 72%, respectively).⁴ Taken together, these results support the findings of the current study, and it is noteworthy that despite population differences, the studies consistently demonstrated a similar relationship between adherence and glycemic control.

The United Kingdom Prospective Diabetes Study demonstrated that reducing A1C in patients with diabetes by 1% decreased the risk of any diabetes-related complications by 21%, death related to diabetes by 21%, and the incidence of myocardial infarction by 14%.²⁰ Because any improvement in glycemic control across the diabetic range is likely to reduce the risk of diabetic complications,²⁰ improved medication adherence to facilitate achievement of glycemic control has important consequences for long-term outcomes in patients with type 2 diabetes.

Although this study provides valuable information about diabetes management in a real-world setting, several limitations are important to consider. Many variables were unavailable for study inclusion, including the severity and duration of type 2 diabetes, patient racial/ethnic background, body mass index, information on patient dietary habits, and frequency of patient glucose self-monitoring. We studied patients from a managed care plan in Oregon; because this study did not include a geographically diverse population, it may be difficult to generalize findings to the US population.

Because our study included patients enrolled in a managed care organization, study findings may not be applicable to patients without health insurance. Medication adherence was measured by patient prescription refills and not drug consumed by the patient; however, other studies have shown that these are highly correlated and have supported the use of pharmacy claims data for the evaluation of these metrics.^{17,21} Despite these limitations, this study provides valuable information in support of the literature that suggests a relationship between adherence and glycemic control in a real-world setting, and underscores the importance of medication adherence in diabetes management.

CONCLUSION

Overall, study findings indicated good adherence with ODMs in this managed care population with diabetes. An association was found between ODM adherence and glycemic control, such that each 10% increase in ODM adherence was associated with a 0.1% decrease in A1C. These findings highlight the importance of medication adherence for attaining glycemic control, thus reducing the incidence of diabetes complications. Initiatives targeting improved medication adherence in patients with type 2 diabetes are important to patient care and health plans.

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Author Affiliations: From Providence Physician Division, Beaverton, Ore (YR, JSH); Novartis Pharmaceuticals Corporation (CP), East Hanover, NJ; and Novartis Pharmaceuticals Corporation (KSW), San Marino, Calif.

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interest with any entity that would pose a conflict of interest with the subject matter of this article.

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Address correspondence to: Yelena Rozenfeld, MPH, Providence Physician Division, 3601 Murray Blvd, Ste 45, Beaverton, OR 97005. E-mail: yelena.rozenfeld@providence.org.

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