Brief Report

Adherence to Oral Antidiabetic Therapy in a Managed Care Organization: A Comparison of Monotherapy, Combination Therapy, and Fixed-Dose Combination Therapy

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ABSTRACT

Background: Although medication adherence is one of the most important aspects of the management of diabetes mellitus, low rates of adherence have been documented.

Objective: This study sought to examine medication adherence among patients with diabetes mellitus in a managed care organization who were receiving antidiabetic monotherapy (metformin or glyburide), combination therapy (metformin and glyburide), or fixed-dose combination therapy (glyburide/metformin).

Methods: Medication adherence was evaluated through a retrospective database analysis of pharmacy claims. The adherence rate was defined as the sum of the days' supply of oral antidiabetic medication obtained by the patient during the follow-up period divided by the total number of days in the designated follow-up period (180 days). Health plan members were included in the analysis if they had an index pharmacy claim for an oral antidiabetic medication between August 1 and December 31, 2000, were continuously enrolled in the health plan, and were aged ≥18 years. A 6-month pre-index period was used to classify patients as newly treated or previously treated. Patients were grouped according to their medication-use patterns.

Results: After adjustment for potential confounding factors, including overall medication burden at index, there were no significant differences in adherence rates among 6502 newly treated patients receiving monotherapy, combination therapy, or fixed-dose combination therapy. Among the 1815 previously treated patients receiving glyburide or metformin monotherapy who required the addition of the alternative agent, resulting in combination therapy, adherence rates were significantly lower (54.0%; 95% CI, 0.52–0.55) than in the 105 patients receiving monotherapy who were switched to fixed-dose combination therapy (77.0%; 95% CI, 0.72–0.82). The 59 previously treated pa-

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tients receiving combination therapy who were switched to fixed-dose combination therapy had a significant improvement in adherence after the switch (71.0% vs 87.0%; $P < 0.001$).

Conclusions: In a managed care organization, previously treated patients receiving monotherapy with an oral antidiabetic medication who required additional therapy exhibited significantly greater adherence when they were switched to fixed-dose combination therapy compared with combination therapy. Patients receiving combination therapy who were switched to fixed-dose combination therapy exhibited significantly greater adherence after the switch.

Key words: oral antidiabetic medication, fixed-dose combination therapy, adherence, diabetes mellitus, compliance. (*Clin Ther.* 2002;24:460–467)

INTRODUCTION

The prevalence of diabetes is escalating at a rapid rate. In the United States, ~16 million adults have diabetes mellitus and a third of cases are undiagnosed. Among US adults aged ≥20 years, the prevalence of diabetes is 8.2%, affecting 7.5 million men and 8.5 million women. According to the Centers for Disease Control and Prevention, 798,000 new cases are diagnosed each year. Although all races are affected, the occurrence of diabetes is 2 to 3 times more likely in the black, Hispanic, and Native American populations.[1]

Substantial economic and societal costs are incurred as a result of diabetes. The sixth leading cause of mortality in the United States, diabetes causes ~160,000 deaths each year.[1] It is second only to cancer in chronic disease costs, most of them the result of major diabetes-related complications. According to the American Diabetes Association, the total cost of diabetes in 1997 was $98 billion, of which $54 billion was in indirect costs related to disability, lost workdays, and premature mortality.[2] In that same year, the direct costs of diabetes for inpatient hospital and nursing home care represented 5.8% of total personal health care expenditures.[2] Additionally, based on data from the National Health Interview Survey,[3] 23.8% of diabetic adults had >1 hospitalization during the previous year, compared with 7.8% of nondiabetic individuals.

The goal of diabetes treatment is to prevent diabetes-related sequelae by achieving and maintaining glycemic control while minimizing adverse events. The American Diabetes Association guidelines set target glycosylated hemoglobin (HbA_{1c}) values at <7% and fasting plasma glucose (FPG) levels at <130 mg/dL for effective management of diabetes.[4] In the United Kingdom Prospective Diabetes Study,[5] patients with FPG concentrations of 108 to 270 mg/dL were randomized to 2 study arms: maximal sulfonylurea (SU) + metformin (n = 317) and maximal SU only (n = 326). The results showed that patients receiving the combination of SU + metformin achieved better glycemic control than did those receiving SU alone. At 3 years, significantly more patients in the SU + metformin group had achieved an HbA_{1c} value <7% compared with patients in the SU monotherapy group (69% vs 48%; $P = 0.007$), and the incidence of hyperglycemia was significantly lower in this group (7% vs 36%; $P < 0.001$). The median FPG concentration declined by 8.5 mg/dL (to 155 mg/dL) in the SU + metformin group, compared with an increase of 8 mg/dL (to 178 mg/dL) in the SU monotherapy group.

Successful control of diabetes requires appropriate diet and nutrition, physical activity, and antidiabetic medication. Although medication adherence is one of the most important aspects of the diabetes treatment regimen, several studies have documented low rates of adherence. Venturini et al[6] reported that ~20% of patients did not take sufficient amounts of their medication for adequate control of blood glucose levels. Skaer et al[7] estimated that 10% to 30% of patients with non–insulin-dependent diabetes discontinued their prescribed medication regimen within 1 year of diagnosis.

The primary objective of the present study was to examine rates of adherence to oral antidiabetic medication among patients receiving monotherapy, combination therapy, or fixed-dose combination therapy in a large managed care organization.

MATERIALS AND METHODS

This was a retrospective database analysis using pharmacy claims from a pharmacy-benefit and medical-management company serving a large managed care organization (~2.5 million covered individuals). The population included patients from California, Oregon, Washington, Texas, and Oklahoma. Members included in the analysis had a pharmacy claim for an oral antidiabetic medication during the identification period (August 1–December 31, 2000), were continuously enrolled in the health plan during the study period, and were aged ≥18 years.

Patients were classified as newly treated or previously treated. Newly treated patients were defined as those who had no fills of antidiabetic medications for 6 months before the index date. Previously treated patients were defined by receipt of antidiabetic monotherapy or combination therapy for at least 6 months before the index date.

Patients identified as newly treated were stratified as follows: (1) those receiving monotherapy with metformin or glyburide; (2) those receiving combination therapy with metformin and glyburide; and (3) those receiving combination therapy with fixed-dose glyburide/metformin. Previously treated patients were stratified as follows: (1) those receiving metformin or glyburide monotherapy both before and after the index date; (2) those receiving metformin or glyburide monotherapy in the pre-index period who had the alternative agent added, resulting in combination therapy, at the index date; (3) those receiving metformin or glyburide monotherapy in the pre-index period who were switched to fixed-dose glyburide/metformin combination therapy at the index date; and (4) those receiving metformin and glyburide combination therapy who were switched to fixed-dose glyburide/metformin combination therapy at the index date. An additional group, those receiving metformin hydrochloride extended-release tablets, was too small (n = 9) and was therefore not included in the analysis.

The index date was defined as the first prescription fill during the identification period, and each patient was followed for 180 days thereafter. For previously treated patients receiving monotherapy, the index date was defined as the first fill during the identification period. However, for those whose therapy was added to, resulting in combination therapy, or switched to glyburide/metformin combination therapy, the index date was the date of the addition or switch. Patients were deemed to be receiving combination therapy in the pre-index period if

they received concurrent treatment with metformin and glyburide (filled within 30 days of each other) and had at least 1 additional fill of each of the concurrent medications before the index date.

Measures of Adherence and Disease Status

The rate of adherence to drug therapy was defined as the sum of the days' supply of oral antidiabetic medication obtained by the patient during the follow-up period divided by the total number of days in the designated follow-up period (180 days). If it exceeded 180 days, the total number of covered days was truncated to 180 days.

The medication possession ratio (MPR) is a proxy measure of medication adherence in the period between the first and last prescription fills. It is defined as the sum of days' supply for all fills divided by the number of days of therapy between the first and last fills plus days' supply for the last fill. This calculation can result in an MPR that exceeds 1.0. When this occurred, the MPR value was truncated to 1.0. Use of both adherence rate and MPR allowed for variability in patient follow-up data.

The chronic disease score (CDS)[8] is a useful measure of comorbidities and health status. Using population-based automated pharmacy data, the developers of the CDS examined the pattern of prescription use during a 1-year period among enrollees in a large health maintenance organization and created a comorbidity index based on weighted therapeutic classes. The CDS is based on the number of chronic diseases and complexity of the medication regimen; thus, the higher the CDS, the greater the burden of comorbidity.

Statistical Methods

All data manipulation and statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Analysis of variance, *t* tests, or chi-square tests were used to compare all unadjusted demographic, clinical, and medication characteristics. Analysis of covariance was performed to compare differences between cohorts. Each of the models was adjusted for age, sex, CDS, insulin use, and total number of tablets taken per day at the index date. For each model, interaction terms of covariances were checked and were included when significance was found. All reported *P* values are 2-sided, with an α of 0.05. Data are presented as mean ± SD.

RESULTS

Newly Treated Patients

A total of 6502 eligible newly treated patients were included in this analysis, 3216 (49.5%) men and 3286 (50.5%) women. Their mean (±SD) age was 62.5 ± 14.8 years, and their mean CDS was 6.1 ± 3.1. Of these, 2898 (44.6%) had commercial insurance, and 3604 (55.4%) had Medicare+Choice insurance. The total medication burden (excluding study medications) was 3.8 ± 3.8 at the index date and 4.5 ± 3.6 at the end of the study.

As described earlier, newly treated patients were stratified into the following cohorts: metformin monotherapy; glyburide monotherapy; metformin and glyburide combination therapy; and fixed-dose glyburide/metformin combination therapy. Of the 6502 newly treated patients, 4545 (69.9%) were prescribed metformin monotherapy, 1651 (25.4%) were prescribed glyburide monotherapy, 219 (3.4%)

were prescribed metformin and glyburide combination therapy, and 87 (1.3%) were prescribed fixed-dose glyburide/metformin combination therapy.

After adjustment for possible confounding factors, including overall medication burden at index, there were no significant differences in adherence over the initial 6 months of pharmacologic therapy between patients receiving monotherapy or combination therapy compared with those receiving fixed-dose combination therapy.

Previously Treated Patients

Monotherapy

A total of 35,487 eligible previously treated patients were included in this analysis, 17,766 (50.1%) men and 17,721 (49.9%) women. Their mean (±SD) age was 67.0 ± 12.5 years, and their mean CDS was 6.5 ± 2.9. Of the total, 11,528 (32.5%) patients had commercial insurance and 23,959 (67.5%) had Medicare+Choice insurance. The total medication burden (excluding study medications) was 4.3 ± 3.8 at index and 4.8 ± 3.6 at the end of the study.

Previously treated patients receiving monotherapy were stratified into the following cohorts: metformin or glyburide monotherapy in both the pre- and post-index periods; metformin or glyburide monotherapy during the pre-index period with the alternative agent added at the index date, resulting in combination therapy; and metformin or glyburide monotherapy during the pre-index period with a switch to fixed-dose glyburide/metformin combination therapy at the index date. Of 35,487 patients, 33,567 (94.6%) were prescribed metformin or glyburide monotherapy; 1815 (5.1%) were prescribed metformin or glyburide and had the alternative agent added, resulting in combination therapy; and 105 (0.3%) were prescribed metformin or glyburide monotherapy and were switched to fixed-dose glyburide/metformin combination therapy.

Differences in medication adherence in this cohort were compared by multivariate analysis, with adjustments for age, sex, CDS, total number of tablets per day at the index date (excluding target drugs), and insulin use. After adjustment for possible confounding factors, significantly lower adherence rates were observed in patients receiving metformin or glyburide monotherapy in the pre-index period who had the alternative agent added, resulting in combination therapy, at the index date (54.0%; 95% CI = 0.52–0.55) compared with those with a switch to fixed-dose glyburide/metformin combination therapy at the index date (77.0%; 95% CI = 0.72–0.82) (Figure 1). Significant predictors of adherence were age <55 years (P = 0.001) and total number of tablets per day, excluding target drugs, at index date (P = 0.024).

Combination Therapy

A total of 59 previously treated patients, 30 (50.8%) men and 29 (49.2%) women, had been receiving combination therapy and were switched to fixed-dose combination therapy. This cohort had a mean (±SD) age of 62.5 ± 12.8 years and a mean CDS of 6.8 ± 2.9; 31 (52.5%) patients had commercial insurance, and 28 (47.5%) had Medicare+Choice insurance.

At the end of the study period, there was a significant improvement in adherence rates in patients who had been receiving combination therapy in the pre-index period and were switched to fixed-dose combination therapy at the in-

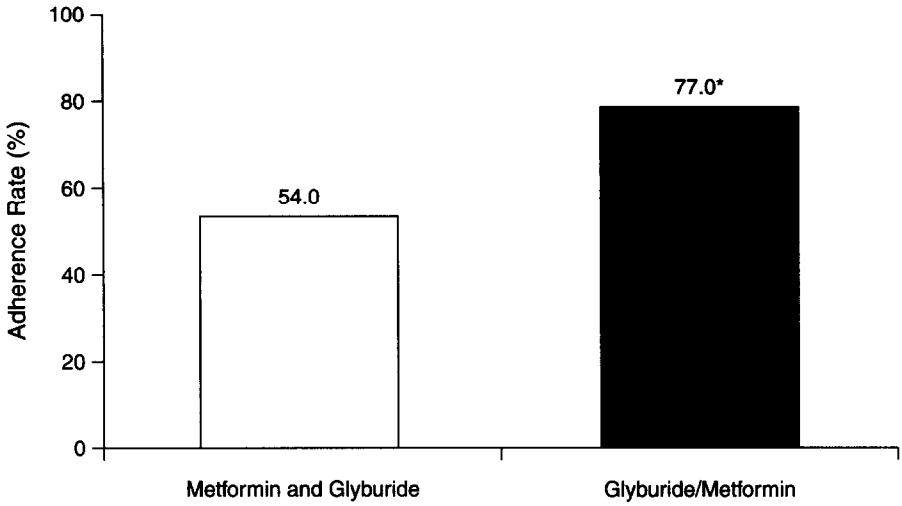

Figure 1. Comparison of adjusted adherence rates in patients receiving metformin and glyburide combination therapy and those receiving fixed-dose glyburide/metformin combination therapy. $^{*}P < 0.001$.

dex date (71.0% vs 87.0%; $P < 0.001$) (Figure 2).

DISCUSSION

The primary objective of this study was to compare patterns of antidiabetic medication adherence in patients receiving fixed-dose combination therapy with those in patients receiving monotherapy or combination therapy. Among newly treated patients, there was no significant difference in adherence between patients receiving monotherapy, combination therapy, or fixed-dose combination therapy. This lack of difference in rates of adherence may be attributed to the impact of receiving a new diagnosis of chronic disease—during the initial 6 months of therapy, the motivation to comply with therapy is likely to be high, irrespective of the daily prescribed medication burden.

It is not surprising that previously treated patients, who might be expected to be better informed about diabetes and its complications, maintained greater rates of adherence than newly treated patients, despite their more numerous comorbidities and their greater medication burden per day. Previously treated patients receiving monotherapy, whether in the form of a single agent or fixed-dose combination therapy, exhibited relatively high adherence rates. When a second medication was added to the regimen of previously treated patients who had been receiving monotherapy, adherence dropped significantly. Thus, fixed-dose combination therapy may be an appropriate treatment alternative when a patient requires greater glycemic control, as the patient would receive the benefit of the additional medication without risking poorer adherence as the result of an increased medication burden.

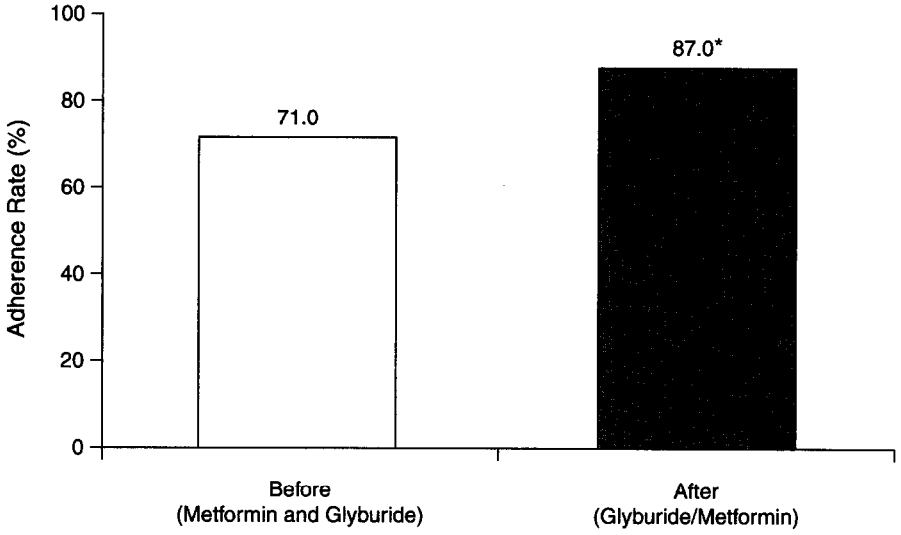

Figure 2. Comparison of adjusted adherence rates before and after the switch from metformin and glyburide combination therapy to fixed-dose glyburide/metformin combination therapy. $^{*}P < 0.001$.

Potential study limitations suggest that the findings be interpreted with caution. There were differences within cohorts in terms of age at index date and CDS. For example, patients receiving glyburide monotherapy were older and had a higher mean CDS than patients receiving fixed-dose combination therapy. Multivariate analyses were performed to adjust for these differences; however, the results may have been influenced by other clinical characteristics that were not similarly accounted for. Additionally, laboratory values such as HbA_{1c}, fasting blood glucose levels, and postprandial blood glucose levels would have been helpful in determining severity of disease.

The adherence rate and MPR were used as proxy measures of compliance. Therefore, it cannot be assumed that because prescription claims were submitted, representing use of oral antidiabetic therapy, the patient actually consumed the medication or consumed it as prescribed. Similarly, it cannot be assumed that an association between process measures (eg, adherence rate and MPR) will necessarily result in improved clinical outcomes (eg, improved glycemic control). Finally, patients were followed for 6 months after an addition to or switch in therapy. It is not certain whether improved compliance continued beyond this period.

CONCLUSIONS

In a managed care organization, previously treated patients with diabetes who were receiving monotherapy with metformin or glyburide and then had the alternative agent added to their regimen, resulting in combination therapy, exhibited significantly lower adherence rates than did those who were receiving mono-

therapy and were switched to fixed-dose glyburide/metformin combination therapy. Previously treated patients receiving combination therapy who were switched to fixed-dose combination therapy exhibited significantly greater adherence rates after the switch. These findings suggest that for patients requiring the combination of metformin and glyburide, a switch to fixed-dose glyburide/metformin therapy may be an appropriate option with the possibility of enhanced adherence. As initial therapy, fixed-dose glyburide/metformin combination therapy did not appear to affect adherence over the initial 6 months of therapy, perhaps due to increased adherence associated with a new diagnosis of a chronic condition and newly prescribed pharmacologic therapy.

Fixed-dose glyburide/metformin combination therapy demonstrated clear adherence benefits among the patients who had received previous treatment with oral antidiabetic medication. Improved adherence may lead to better glycemic control, thereby reducing the incidence of potential complications associated with diabetes.

ACKNOWLEDGMENT

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