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# HYPOGLYCEMIC DRUG UTILIZATION AND ADHERENCE TO PRESCRIBED REGIMENS: A PHARMACOEPIDEMIOLOGIC STUDY USING RETAIL PHARMACY DATA

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# HYPOGLYCEMIC DRUG UTILIZATION AND ADHERENCE TO PRESCRIBED REGIMENS: A PHARMACOEPIDEMIOLOGIC STUDY USING RETAIL PHARMACY DATA

BY

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## ABSTRACT

Diabetes mellitus is a highly prevalent condition, afflicting an estimated 6% of the United States adult population. It is also a complex condition to manage. Dietary, exercise, and drug therapies are essential for reducing the risk of various neurologic and vascular diseases related to disease progression. Tight control of blood glucose as achieved through intensive pharmacologic therapy has been shown to decrease the risk of developing several types of diabetic complications. Success in achieving tight blood glucose control is contingent upon adherence to the prescribed hypoglycemic drug regimen, a behavior known to often be sub-optimal.

The objectives of this study were a) to describe hypoglycemic drug utilization, and compare drug regimens prescribed and costs among age groups, insurance plans, and by gender; b) to assess adherence to prescribed hypoglycemic therapies, and to explore the association between nonadherence and change in the strength or type of hypoglycemic medication prescribed; and c) to identify the frequency of nonadherence among patients who are prescribed monotherapy with a sulfonylurea or metformin, as compared to the frequency of nonadherence in patients who are prescribed dual therapy with both medications.

Analyses were performed using retail pharmacy data. The data provided included over one-quarter-million dispensings to 5056 diabetic patients. From this population, 2901 patients that received at least 2 dispensings for a hypoglycemic medication during a 12-month period were selected for study.

Sulfonylureas were the mainstay of treatment for those receiving oral therapy: 82% of patients received a sulfonylurea as monotherapy or in combination with another hypoglycemic medication. The most frequently observed drug regimen was sulfonylurea monotherapy (40.3%); followed by insulin use only (24.9%); dual therapy with sulfonylurea plus metformin (13.9%); and metformin monotherapy (6.96%). Differences in the drug regimen utilized were found among age groups and between genders. Most notably, sulfonylurea monotherapy was prescribed most frequently for patients 65 years of age and older (age 65 years or older: 48.4%; age 50-64: 43.6%; age under 50: 30.8%, $p < 0.0001$). The 12-month cost of hypoglycemic medication dispensed was lowest among patients 65 years of age or older.

The medication possession ratio (MPR) was used as an estimate of adherence. Possession of medication was found to be associated with a change in the strength or type of hypoglycemic medication dispensed. Sulfonylurea users who failed to possess medication for at least 80% of days during a four-month period were 41.7% more likely to receive a dispensing for a different strength of medication in subsequent months, as compared with

those possessing medication for at least 80% of days (OR 1.42, 95% CI 1.02 – 1.96). Additionally, among patients receiving either monotherapy with a sulfonylurea or metformin, those possessing medication for at least 80% of days were 36.4% more likely than those possessing at least enough medication for 80% of days to receive a dispensing for a different strength of medication (OR 1.36, 95% CI 1.019 – 1.83), or for a different strength or type of hypoglycemic medication (OR 1.39, 95% CI 1.03 – 1.87). This finding was not statistically significant in the smaller sample of patients receiving monotherapy with metformin.

Medication possession was also found to be associated with the number of hypoglycemic drugs prescribed. Patients who were prescribed a regimen of dual therapy with a sulfonylurea plus metformin were found to be less likely to possess medication for 80% or 90% of days, as compared with those prescribed monotherapy with either a sulfonylurea or metformin. In multivariate analyses controlling for age and the total number of dispensings, patients receiving dual therapy were more than 3 times more likely to fail to possess medication for at least eighty percent of days (OR 3.14, 95% CI 2.42 – 4.08), or 90% of days (OR 3.20, 95% CI 2.49 – 4.11).

The findings of this pharmacoepidemiologic research provide insight into the drug utilization patterns of diabetic patients. Among patients in this study, the type of drug regimen prescribed differed in frequency among age groups and

between genders. The strength and type of hypoglycemic medication utilized was found to change frequently, particularly among patients that were classified as nonadherent. Overall, a substantial percentage of patients were found to be nonadherent with hypoglycemic drug therapy. Patients least frequently adherent to drug therapy included those under 65 years of age and those prescribed dual therapy with a sulfonylurea plus metformin. Presuming that lack of medication possession results in poor glucose control, patients who do not possess medication are at increased risk for diabetic complications.

## ACKNOWLEDGEMENTS

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## PREFACE

This dissertation is organized using the manuscript format. Part 1 consists of three studies that form the main body of the dissertation. Part 2 contains the appendices which provide details required by the University but are not usually presented in a published paper.

Part 1:

Study 1: Hypoglycemic Drug Utilization in a Diabetic Population: A Pharmacoepidemiologic Study Using Retail Pharmacy Data

Study 2: Changes in Oral Hypoglycemic Therapy: Influence of Nonadherence as Determined by Medication Possession

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**Study 2: Changes in Oral Hypoglycemic Therapy: Influence of Nonadherence as Determined by Medication Possession**

# PART 1

Part 1 includes the following manuscripts:

Study 1: Hypoglycemic Drug Utilization in a Diabetic Population: A Pharmacoepidemiologic Study Using Retail Pharmacy Data

Study 2: Changes in Oral Hypoglycemic Therapy: Influence of Nonadherence as Determined by Medication Possession

Study 3: Adherence to Hypoglycemic Therapy among Patients Prescribed Monotherapy with a Sulfonylurea or Metformin, and Dual Therapy with Both Agents

**Hypoglycemic Drug Utilization in a Diabetic Population: A Pharmacoepidemiologic Study Using Retail Pharmacy Data**


## ABSTRACT

**Background** For most diabetic patients, pharmacologic therapy is an essential component of disease management. Several classes of hypoglycemic medications are available for prescribing, with no single class of hypoglycemic drugs has been proven superior in reducing diabetic complications.

**Objective** To describe hypoglycemic drug utilization patterns among diabetic patients; and to determine if such patterns differ by patient characteristics.

**Methods** Cross-sectional descriptive study of hypoglycemic medication dispensings to 2901 diabetic patients. Drug utilization was classified into categories representing 10 various hypoglycemic drug regimens. The frequency of drug regimen utilization was compared by age group, insurance plan, and between genders. The total cost of hypoglycemic dispensings during a 12-month period was also determined, and compared within each age group and insurance plan, and between genders.

**Results** The most frequent hypoglycemic drug regimen utilized was monotherapy with a sulfonylurea (n = 1168; 40.26%). Use of insulin and no oral hypoglycemic medication was the second most frequently utilized regimen (n = 723; 24.92%). Dual therapy with both a sulfonylurea and metformin was utilized by 13.93% of patients (n = 404). No other regimen was observed at a frequency greater than 5 percent. A substantial percentage of patients received a dispensing for troglitazone (16.04% of all patients over 40 years of age), mostly in combination with other medications. Patients 65 years of age and older more frequently received dispensings for a sulfonylurea only (age 65 years or older: 48.4%; age 50-64: 43.6%; age under 50: 30.8%, $p < 0.0001$), but not for dispensings for a sulfonylurea and metformin (age 65 years or older: 14.4%; age 50-64: 15.2%; age under 50: 15.6%, $p < 0.8275$). Older patients also less frequently received dispensings for only metformin (age 65 years or older: 4.8%; age 50-64: 7.9%; age under 50: 7.2%, $p < 0.0.476$), and for troglitazone (age 65 years or older: 10.28%; age 50-64: 17.6%; age under 40-49: 20.3%, $p < 0.0001$). Female patients more frequently received dispensings for only insulin (28.1% versus 22.2%, $p = 0002$). Male patients received only a sulfonylurea more frequently than female patients (44.1% versus 35.8%, $p< 0.0001$). The hypoglycemic drug regimen utilized did not differ significantly by insurance plan for the most frequently utilized regimens and between the two main insurers included in this study. The 12-month cost of hypoglycemic drug utilization was lowest among patients 65 years of age or

older (age 65 years or older: $470.38; age 50-64: $593.23; age under 50: $580.80, Pr > F less than 0.0001).

**Conclusions** We found sulfonylureas to be the mainstay of treatment for the majority of patients receiving oral therapy. Patients 65 years of age and older were less frequently dispended troglitazone, or metformin in mono-therapy, and were most frequently prescribed sulfonylureas as the only hypoglycemic medication. For patients 65 years of age or older, the 12-month cost of hypoglycemic medications dispensed was roughly 20% less than the average hypoglycemic drug utilization cost for younger diabetic patients. Differences in drug utilization among senior patients may reflect differences in co-morbidities that influence drug selection, differences in insurance coverage and associated out-of-pocket costs, or perhaps reluctance of prescribers to utilize newer therapies in older diabetic patients. Further research is needed to determine if older patients are less frequently prescribed newer therapies, and if diabetes control and progression is impacted.

## INTRODUCTION

Diabetes mellitus has been identified as an epidemic throughout the world (1-15). Approximately 16 million Americans are afflicted with the condition, a prevalence rate that exceeds 6% of the United States population (16). The number of Americans living with diabetes has increased steadily. Based upon data from the US National Health Interview Surveys, the prevalence of diabetes has grown in a near-linear manner, rising from under 1% in 1958 to approximately 7% in 1993 (17). Recently, Mokdad et al reported that the prevalence rate of diabetes increased 33% from 1990 to1998 (4.9 to 6.5%) (18). The number of Americans living with diabetes is expected to double by 2020, and the disease is expected to become more prevalent in younger age groups (19).

Positive family history (20-22), older age (23-26), and obesity (27-29) are associated with an increased risk of developing diabetes. The rise in diabetes prevalence reflects the growing number of older adults in the US population, and is compounded by an increased rate of the disease in this population (17). An increasing prevalence of obesity among Americans of all adult ages has also contributed to the rise in diabetes prevalence (30). Diabetes has a major impact on the health of those afflicted with the condition. Diabetes is the seventh leading cause of death among U.S. citizens (31), and contributes

significantly to other leading causes of death such as cardiovascular disease (32, 33), stroke (34), and kidney failure (35-37).

Type 2 diabetes, formerly termed adult-onset or non-insulin dependent diabetes mellitus, accounts for roughly 90% of all cases of diabetes (17). Patients with type 2 diabetes mellitus generally develop the condition after the age of thirty (20), and are usually managed with oral hypoglycemic medications when dietary therapy and exercise fail to control blood glucose levels. Sulfonylureas, discovered in 1942 by Janborn (38), have long been the mainstay of type 2 diabetes treatment. During the past several years newer oral therapies have become available, which exert a hypoglycemic effect through differing biological mechanisms. These agents have been approved for use in combination with other medications (39-45) or, for some drugs, for use as mono-therapy (40, 43 - 45).

The choice of oral hypoglycemic medication may reflect patient characteristics. For example, metformin has been shown to be particularly efficacious in patients with obesity (46), and sulfonylureas may cause rash in some patients (47). However, despite the several classes of hypoglycemic medications to choose from, specific guidelines or algorithms for selection of drug therapy in type 2 diabetic patients are lacking. For example, the American Diabetes Association's 2001 Clinical Practice Recommendations (48) include specific goals of pharmacologic therapy; including reduction of glycated hemoglobin

(HbA1c) to below 7%. However, the choice of hypoglycemic agent is left to the prescriber. Thus, the choice of anti-diabetic agent utilized can be largely determined by prescriber preferences and experiences. Further, despite the availability of numerous studies assessing the glycemic control achieved with various hypoglycemic drugs, there is scant comparative data describing primary outcomes among diabetic patients prescribed alternative hypoglycemic drug classes.

We examined hypoglycemic drug utilization in a large diabetic population, using data obtained from retail pharmacies during a 24-month period. We determined the frequency of dispensing of medications, and the characteristics of patients receiving dispensings for specific hypoglycemic agents. Changes in hypoglycemic drug regimen during a 12-month period were determined, including the number of patients switching to a different drug or combination of drugs. The average cost of hypoglycemic medications dispensed during a 12-month period was calculated, and compared between age groups, gender, and insurance types.

## METHODS

### Data source and study population

Consumer Value Stores (CVS), Inc provided data from 198 retail pharmacies throughout Pennsylvania. The data included all pharmacy claims for 5056 diabetic patients from April, 1997 – May, 1999. The total number of pharmacy dispensings for these patients during the 2-year period was 288,171.

All patients were enrolled in a comprehensive diabetes management program through one of two health insurance plans. Pharmacy services for these patients were provided by CVS pharmacies, and patients were not reimbursed for prescriptions filled by other pharmacies. Thus, the data represents patients' utilization of hypoglycemic drugs, though some patients may have filled prescriptions elsewhere using a different third party plan for drug reimbursement, or by paying cash.

To create a standard basis of comparison, we included only patients who were dispensed at least 2 prescriptions over a time period spanning at least 12 months. This was accomplished by determining the number of days between the first and last dispensing of any hypoglycemic medication during the two-year period for which data was available. Of the 5056 patients in the population, 2901 patients (57.4%) met this criteria. For these patients, a

sample was created that included only the first 12-months of hypoglycemic drug dispensings. This sample was used for all analyses.

Hypoglycemic medications were categorized by therapeutic class, or by generic name if the drug was the only available product of its class. The following categories were created: insulin, sulfonylurea, metformin, alpha-glucosidase inhibitor, meglitinide, glimepramide, and troglitazone (Rezulin®), the first available drug from the thiazoladinedionne class. The study period preceded the withdrawal of troglitazone from the U.S. market, and also preceded the introduction of two newer thiazoladinedionne agents to the US market: pioglitazone (Actos®) and rosiglitazone (Avandia®).

Patients were categorized as receiving one of ten hypoglycemic drug regimens, based upon the class(es) of hypoglycemic agent prescribed during the first 90 days of the 12-month period. These drug regimens are presented in Figure 1. For comparison, we also categorized drug regimens based upon hypoglycemic agents dispensed during the last 90 days of the 12-month period.

For all patients, we determined the age, gender, and insurance plan associated with prescription dispensings. Age was categorized into three groups: less than 50; 50-65; and 65 years or older. To enhance the focus on drug regimens used by type 2 diabetics, some analyses were performed

restricting the population to those 40 years of age or older, to exclude patients likely to be type 1 diabetics. The two major insurers included in this study were classified as health plan A and health plan B. Patients were categorized as enrollees of health plan A or health plan B if any prescription dispensed during the 12-month period was associated with a reimbursement claim to either of these insurers. In instances where both insurances were used during the 12 month period, the insurance type associated with first hypoglycemic drug dispensing was used. A smaller number of patients used other insurances for their prescription drug coverage. These patients were included in a third category consisting of all 'other insurances'. A fourth category included patients that paid cash for their hypoglycemic medication prescriptions during the 12-month period.

For dispensings of sulfonylureas, we also categorized agents as first generation sulfonylureas (chlorpropamide, tolazamide, and tolbutamide) or second-generation sulfonylureas (glyburide or glipizide), and into groups of brand name and generic products. The use of these agents among different age categories was determined.

We calculated the total cost of all hypoglycemic medication dispensed during the 12-month period, and compared this cost between genders, age categories, and insurance types. Cost was calculated as the average wholesale price (AWP) of medication dispensed minus 10 percent. Generally,

drug purchasers pay AWP minus a discount rate for drugs, which can be influenced by factors such as the quantity of medication purchased (49). We considered AWP-10% to be a relatively conservative estimate of the cost of drug dispensed, representing the highest amount a drug purchaser would typically pay (50-52).

**Statistical analyses**

Descriptive statistics were used to determine and present gender, age category, and insurance type. Drug regimens utilized and changes in drug regimen were presented as frequencies and percentages. Non-parametric (chi-square) analyses were used to determine if the frequency of drug regimen utilized differed in statistical significance by the gender, age category, and insurance type of subjects. Chi-square tests were also to determine differences in dispensing of brand name products and first generation sulfonylureas among age groups, gender, and insurance types; and to determine differences in the frequency of troglitazone dispensing in the three age groups.

Analysis of variance procedures using Tukey's test were used to determine if differences in 12-month hypoglycemic drug utilization costs among age groups and insurance types were statistically significantly different. We used the student's t-test for independent samples to determine if hypoglycemic drug spending differed by gender.

Statistical analyses were performed using SAS for windows version 8.01.

## RESULTS

### Descriptive statistics

A total of 2901 patients received hypoglycemic drugs spanning at least a 12-month time period. Of these patients, 1002 (34.54%) were under 50 years of age; 1259 (43.4%) were between 50 and 65 years of age; and 640 (22.06%) were 65 years old or older. Slightly more patients were male (n = 1552; 53.5%). One-third of patients (n =967) were insured by health plan A, and 53.84% of patients (n = 1562) were enrollees in health plan B. A smaller percentage of patients (8.62%) used other insurance plans for their prescription coverage, and 4.21% of patients paid for their prescriptions by cash. Nearly one-third of the population were insulin users (n = 890; 30.86%). These statistics are presented in table 1.

### Drug regimen prescribed

Patients were categorized as receiving one of nine potential drug regimens. A tenth regimen category represented miscellaneous combination therapies not captured by the first nine regimen categories. The number and percentage of patients receiving each regimen during the first 90 days of the 12-month period is presented in Table 2a. A comparison of the frequency and percent utilization of drug regimens identified using the first and last 90-days of the 12-month period is presented in Table 2b.

Based upon dispensings during the first 90 days of the 12-month period, the most frequently prescribed hypoglycemic drug regimen was mono-therapy with a sulfonylurea (n = 1168; 40.26%). The 723 patients receiving insulin as their only hypoglycemic medication accounted for next most frequently observed regimen (24.92%). Combination therapy with sulfonylurea and metformin was the only other regimen observed in more than 10% of patients (13.93%; n = 404). Metformin mono-therapy was the fourth most frequently observed hypoglycemic regimen (6.96%; n =202). The prevalence of the other five prescribed regimens ranged from 1.17 to 3.14%. Less than 2 percent of patients received a combination of drugs that was not characterized by any of drug regimen categories 1-9.

Drug regimen classification based upon the last 90 days of the 12-month period produced similar results, though some differences were observed. The order of the top four frequently utilized regimens was the same for drug regimens classified using the first and last 90 days. However, the percent of patients utilizing other regimens differed notably. The percentage of patients receiving a sulfonylurea plus another oral agent other than metformin (regimen 6) more than doubled (6.17% versus 2.65%). Correspondingly, the percentage of patients receiving sulfonylurea mono-therapy during the last 90 days of the 12-month period declined from 40.26% to 31.51%. Also, during the last 90-days, a greater number of patients received a regimen other than one of the 9 identified regimen categories (6.27% versus 1.72%). Utilization of

the other less frequently observed regimens remained similar: the difference in percentage observed ranged from 0.14% - 1.14%.

We determined the number of patients remaining on the same regimen during the two 90-day periods. For patients not utilizing the same hypoglycemic drug regimen in each 90-day period, we identified which regimen patients switched to. These results are presented in Tables 3a (frequencies) and 3b (percentages). Insulin-only users as identified during the first 90-day period were most likely to be classified as utilizing the same regimen in each 90-day period (82%). The regimens with the lowest percentage of patients utilizing the same hypoglycemic regimen in each 90-day period were regimen 2 (insulin + troglitazone (56%)) and regimen 3 (insulin + non-troglitazone agent (30%)), though the total number of patients receiving these regimens was small.

Three-quarters of patients receiving a sulfonylurea, glimepramide, or metformin mono-therapy utilized these same regimens in each 90-day period. Patients receiving mono-therapy with a sulfonylurea, glimepramide, or metformin remained on the same regimen more frequently than patients receiving combination therapy of a sulfonylurea plus another oral agent (remained on mono-therapy with either sulfonylurea, glimepramide, or metformin: 74-75%; remained on sulfonylurea plus metformin: 70%, or remained on sulfonylurea plus non-metformin oral agent: 65%). Half of patients categorized as receiving mono-therapy with troglitazone during the

first 90-days of the 12-month period were utilizing this regimen during the last 90-day period. Of the patients categorized as utilizing an uncategorized combination of hypoglycemic agents (regimen 10) during the first 90-day period, 68% remained in this category when examining the last 90 days of drug dispensings. A greater number of patients utilized an uncategorized drug regimen during the last 90 days as compared to the first 90 days of the 12-month period (232 versus 50).

As compared with male patients, females were more frequently dispensed prescriptions for insulin (28.12% versus 22.2%; $p = 0.0002$) and dispensings for insulin and troglitazone (3.9% versus 2.5%; $p = 0.0386$). Diabetic males were more frequently prescribed sulfonylureas as mono-therapy (44.1% versus 35.8%; $p < 0.0001$). There was no statistically significant difference in the percentage of male and female patients that received combination therapy that included a sulfonylurea. The percentage of male and female patients receiving mono-therapy with metformin, troglitazone, or glimepramide also did not differ significantly. These findings are summarized in Table 4.

Table 5a presents regimen categories stratified by age group. A higher percentage of patients under 50 years of age received insulin as their only hypoglycemic agent, as compared to patients aged 50-64 or 65 or older (36.9% versus 18.4% and 19.1% respectively, $p < 0.0001$). Conversely, the percentage of patients that received only a sulfonylurea was significantly less

for patients under 50 years of age as compared to patients aged 50-64 or 65 or older (30.8% versus 43.6% and 48.4%, $p < 0.0001$).

To focus on drug prescribing in type 2 diabetic patients, we identified drug regimens prescribed for patients over 40 years of age (Table 5b). When patients under 40 years of age were excluded from the analysis, the percentage of patients using insulin as their sole hypoglycemic agent was no longer statistically significantly different among age groups. However, subjects in the 40-49 age group were more frequent users of insulin plus troglitazone combination therapy (5.0% versus 3.3% and 1.4%; $p = 0.0013$), though there was a relatively small number or total patients receiving this regimen (91/2901; 3.14%). The youngest age group remained the least frequent users of a sulfonylurea mono-therapy regimen (39.6% versus 43.6% and 48.4%; $p = 0.0067$). Diabetics 40-49 years of age were also more likely to be prescribed metformin compared to patients over 65 years of age (9.1% versus 4.8%; $p = 0.0107$).

We also examined the relation between insurance type and drug regimen utilized. Table 6 presents percentages of patients receiving each drug regimen, stratified by four categories of payment: Plan A, Plan B, other insurance, and cash payment. There was no statically significant difference in the percentage of patients utilizing regimens of insulin only, insulin plus an oral agent, sulfonylurea mono-therapy, or sulfonylurea plus a non-metformin oral

agent. Patients not utilizing insurance (paying cash) were less frequently dispensed regimens that included metformin (metformin mono-therapy: cash 2.5%, plan A: 6.5%, plan B: 4.0%, other insurance types: 8.4%; $p = 0.0107$; metformin plus sulfonylurea: cash 9.8%, plan A 11.8%, plan B 15.8%, all other insurance types: 12.8%; $p = 0.0187$. Also, a lesser percentage of Plan B patients received mono-therapy with glimepramide (plan A: 4.3%, plan B: 1.3%, all other insurances: 2.8%, cash: 5.7%; $p< 0.001$)

The percentage of patients receiving a brand name sulfonylurea did not differ in statistical significance among age groups or gender (Table 7). Patients with insurance plan A received brand name products more frequently that patients enrolled in plan B (64.0% versus 41.8%; $p < 0.001$). The percentage of brand name sulfonylureas dispensed was highest among patients paying cash for their prescription (64.6%), although the frequency was only slightly higher than that found for plan A (64.0%). Of patients with insurance other than plan A or plan B, 55.2% of sulfonylurea-using patients received brand name products.

Of the 1575 patients receiving a sulfonylurea, 17 (1.08%) received a first generation product. The frequency of first-generation sulfonylurea utilization did not differ in statistical significance among age groups, gender, or insurance type.

Patients 40-49 years of age were most frequently dispensed troglitazone (20.3%), while those 65 years of age or older were least frequently prescribed this drug (10.1%). The difference in frequency of troglitazone utilization between these age groups was statistically significant ($p < 0.0001$).

Table 9 presents the average cost of all hypoglycemic medications dispensed during the 12-month period for each age category, gender, and insurance type. The average 12-month cost of hypoglycemic medication utilized by patients 65 years of age and older was significantly less than the cost of hypoglycemic medications utilized by younger patients (age 65 and older: $470.37, age 50-65: $593.23, age under 50: $580.80; Pr > F: < 0.0001). The average 12-month hypoglycemic drug utilization cost did not differ significantly between men and women. Average costs were similar among insurance types, but not among patients paying cash. (plan A: $521.63, plan B: $587.82, all other insurances: $523.01, cash: $385.37).

## DISCUSSION

Pharmacy data is a useful and often available information source for pharmacoepidemiologic investigations of drug utilization patterns. Pharmacy data can be used to identify trends in prescribing patterns (53), assess the impact of regulatory changes (54), and to determine drug expenditures (55). Though the lack of information related to patient diagnoses can be limiting (56), pharmacy data can be superior to the medical record for determining if and when prescriptions are actually filled by patients; an action necessary for adherence to therapy. Pharmacy data is an excellent source for describing drug use in populations, and for comparing patterns of use between populations.

In this study, pharmacy data was used to describe the utilization of hypoglycemic drugs in a population of diabetic patients. We created nine categories of drug regimens utilized, based upon the types of hypoglycemic drugs dispensed to patients. We compared the frequency of regimen utilization among age groups, gender, and payment type. Identification of regimen utilized was based upon hypoglycemic drugs dispensed during the first 90 days of a 12-month period, and was compared with the frequency of regimens utilized in the last 90-days of the 12-month period. We identified which patients changed medication regimen, and which different regimen was utilized.

**Frequency of regimen category utilized**

Sulfonylureas, a staple of therapy for type 2 diabetes for several decades, were the most frequently prescribed oral hypoglycemic agent in this population. Factors contributing to the popularity of these agents include a long history of use (38), relatively low expense (57), high tolerability (58), and prescriber familiarity. Metformin was also prescribed frequently in this population, either as mono-therapy or in combination with other oral agents, usually a sulfonylurea. Several oral hypoglycemic agents became available just before or during the study period: troglitazone, acarbose, repaglinide, and glimepramide. Despite the availability of these newer agents, the majority of patients receiving oral hypoglycemic therapy were receiving a sulfonylurea, metformin, or both together. However, the impact of the new thiazoladinedionne drug class was apparent. Troglitazone, the first thiazoladinedionne available in the US market, was the only thiazoladinedionne available for prescribing during the study period. Consistent with its approved indications, troglitazone was utilized as mono-therapy or in combination with insulin or oral hypoglycemic agents. Troglitazone was discontinued in 1999 after awareness of an association with hepatic failure and death among patients prescribed this agent (59-62). The increased risk for liver toxicity in those treated with troglitazone was recognized while the drug was available for prescribing (63), potentially explaining why troglitazone was prescribed less frequently for older patients in this population (Table 7).

Despite the effective treatment of diabetes with sulfonylurea, metformin, or insulin, glycemic control is known to become poorer as diabetes progresses (64-66). Failure of sulfonylurea mono-therapy to control blood glucose levels generally occurs within 5 years (67, 68). In this population, patients changed medication regimens with high frequency; perhaps reflecting increased medication needs to achieve blood glucose control. Though it was the most frequently observed oral hypoglycemic regimen, mono-therapy with a sulfonylurea was the regimen having the largest percentage change during the 12-month observation period (sulfonylurea mono-therapy in first 90 days: 40.26%; in last 90 days: 31.51%). Slightly greater than 10% of patients utilizing sulfonylurea mono-therapy added metformin to their regimen during the 12-month period (Table 3a). Another 5% of patients added an agent other than metformin, and 6% of these patients changed therapy to a combination regimen that did not include a sulfonylurea. These findings suggest that many type 2 diabetic patients do not remain stable on their medication regimens, and that medication requirements increase over time. Indeed, 26.68% of patients (774/2127) were categorized as utilizing a different drug regimen during the last and first 90 day periods of the 12-month period. The finding that one of four patients changed regimen during the 12-month study period is consistent with what is known about diabetes: the condition progresses, it can be unstable, and medication needs increase over time (20).

As compared to utilization based upon the first 90 days of the 12-month period, the utilization of sulfonylurea mono-therapy was less, and the utilization of combination therapies was greater during the last 90-days of the 12-month period. The decrease in sulfonylurea mono-therapy and increase in use of oral combination therapies may be related to several factors. First, it is possible that the increase in utilization of combination regimens is partly the result of increased medication needs associated with disease progression over time. Second, the increased use of combination therapy may reflect the availability of newer hypoglycemic agents approved for use in combination therapies during the 12-month period, such as repaglinide, glimepramide, acarbose, and troglitazone. A third possible influencing factor is the increased awareness and popularity of combination therapy as a means to achieve improved glycemic control.

Of patients categorized as users of insulin as their sole hypoglycemic medication during the first 90 days of the 12-month period, 5% added troglitazone to their regimen during the following 9 months. Another 5% of insulin users added an oral agent other than troglitazone to their regimen.

Differences in hypoglycemic drug utilization between the two 90 day periods may be partly attributed to patient behavior, and may not necessarily represent changes in hypoglycemic drugs prescribed. Non-adherence to prescribed drug regimens is a recognized problem (69-71), and may have caused

misclassification of regimens, since patients must have filled a prescription to be identified as being prescribed the drug. It is also possible that patients may have received medication from another pharmacy, though the data includes all designated pharmacies for patients in health plans A and B. A third possible factor contributing to misclassification of regimens is the possibility that patients received several month-supply of medication shortly before the 90-day categorization period. Such stockpiling would be most likely among cash paying subjects, since health plans A and B allowed only a one-month supply of medication per dispensing. A frequency analysis of days supply dispensed confirmed that one or two month supplies of medications were dispensed to a great majority of patients.

**Frequency of drug regimen utilization by gender, age group, and insurance type**

We compared the frequency of drug regimen utilization among female and male subjects. Women were more frequently prescribed insulin as a sole hypoglycemic therapy ($p = 0.0002$), and women were more frequently dispensed insulin in combination with troglitazone ($p = 0.0386$). This finding, in addition to the less frequent utilization of sulfonylurea mono-therapy regimens, may indicate a greater frequency of type I diabetes among female subjects in this population. However, there was no statistically significant difference in the utilization of other oral hypoglycemic drug regimens between

men and women. Additionally, the frequency of metformin use did not differ in statistical significance among men and women. In sum, women were more frequently dispensed insulin and less frequently dispensed only sulfonylureas; yet the frequency of utilization of other oral regimens did not differ significantly. This observation is not readily explainable.

Those in the under-50 age group were the most frequent users of insulin, likely due to a higher prevalence of type 1 diabetics in this age strata. There was no significant difference in the frequency of insulin-only therapy among age categories when patients under 40 years of age were removed from the analysis. This finding suggested that the proportion of type 1 diabetics in each age group was similar when including only patients 40 years of age or older. Thus, when comparing drug regimens utilized among age groups, differences in the regimen utilized was presumed not to reflect differences in the proportion of type 1 and type 2 diabetics.

We found differences in the frequency of drug regimen utilized by patients 65 years of age or older. First, though there was no statistically significant difference in insulin prescribing among age groups, seniors were less frequently prescribed troglitazone in combination with insulin. Though removed from the US market in 2000 due to risk of life-threatening hepatic injury, troglitazone, the first available thiazoladinedionne, was recommended as a useful agent in the management of diabetes (72-74). Prescribers may

have avoided prescribing troglitazone in older patients due to concern that older patients may be at greater risk for troglitazone-induced hepatic toxicity. Though prescription drug coverage was available to older patients in this population, it is also possible that prescribers avoided prescribing this product in older patients due to financial considerations. The retail price for a 30-day supply of troglitazone exceeded the average one-month cost of a generic sulfonylurea, a regimen utilized with increased frequency among older subjects. Since the cost of the dispensing to the patient (co-payment) was not available, the influence of cost on drug regimen utilization cannot be directly assessed. However, it is interesting that seniors were most frequently prescribed mono-therapy with a sulfonylurea, the oldest and most inexpensive oral hypoglycemic drug regimen available. Additionally, seniors utilized metformin as mono-therapy less frequently, but were not less frequent users of regimens of sulfonylurea plus metformin. Thus metformin was used more frequently as an adjunct to sulfonylurea therapy in seniors. Contrastingly, younger patients were prescribed mono-therapy with metformin more frequently than older patients ($p = 0.0107$). Metformin has been shown to be particularly useful in obese diabetic patients (65). The less frequent use of metformin mono-therapy among seniors may reflect a lower prevalence of obesity among those 65 years of age and older in this population.

We also examined the frequency of drug regimen prescribed for each insurer type. We did not find the frequency of drug regimens prescribed to differ

significantly between the two main insurance plans included in this study. One exception was the use of glimepramide as mono-therapy, which was less frequently prescribed for patients insured by plan B. However, only a small percentage of patients were prescribed this drug as mono-therapy (2.6%; 76/2901). Of the patients that paid cash for their prescription, one-half were prescribed sulfonylurea mono-therapy.

**Additional analyses**

We found a low prevalence of first generation sulfonylurea utilization (1.1%; 17/1168), and older persons were not more frequently dispensed these agents. The infrequent use of these products reflects an awareness of the increased potential for hypoglycemia associated with chlorpropamide (58), and the lower likelihood for adverse effects such as hyponatremia and disulfiram-type reactions (75-77). Use of first-generation sulfonylureas did not differ by age group or by gender. We did not expect to find a difference in dispensings for brand-name sulfonylurea products among age groups or by gender. However, although patients covered by health plan B utilized brand name sulfonylureas less frequently, the average 12-month cost of hypoglycemic drugs dispensed to patients in plan B was the highest of all insurance types. Thus, it appears that factors other than dispensing of generic products were important determinants of drug utilization costs; and may include factors such as the frequency of use of combination therapies, disease severity, or a more frequent use of newer drugs for which generic products are not available.

**Average total 12-month cost of hypoglycemic drugs dispensed**

A major finding of this research was that of all age groups, expenditures for hypoglycemic medications were lowest among patients age 65 or older. The mean 12-month expenditure of $470.38 for seniors differed by more than $100 compared with patients aged 50-64 ($593.23) and less than 50 years of age ($580.80). This finding is consistent with other observations in this study. First, seniors were less frequently prescribed troglitazone in combination with other medications, and were less frequent users of metformin as mono-therapy. Both troglitazone and metformin are higher priced products. Second, seniors were more frequently prescribed mono-therapy with sulfonylureas, a drug class available as generic products that are less expensive than metformin or troglitazone. Though seniors were less frequently prescribed brand name sulfonylurea products (Table 8), the relative difference among groups was small and did not differ in statistical significance. Thus, though the proportion of patients in each age category prescribed generic sulfonylureas was similar, more seniors received generic sulfonylureas as their only hypoglycemic agent.

**Study limitations**

Several limitations of this study can be described. First, this study categorizes drug regimen prescribed based upon medications dispensed during a 90-day period. It is possible that medications were prescribed by the physician but not dispensed by the pharmacy during the 90 day period. For example,

medications received as samples or through special programs were not identified. Further, it may be argued that drugs dispensed during the 90 day period may not accurately reflect hypoglycemic drug utilization during a 12-month period. We felt that using the first and last 90 days of the 12-month period to identify the regimen afforded the opportunity to compare regimens utilized at the start and end of the study period. Using a 12-month period to categorize regimens would have resulted in identification of a large number of miscellaneous regimens: Patients switching regimens during the year would have been considered users of all hypoglycemic drug types dispensed during the 12-month period. Another limitation relates to the use of other pharmacies. Prescriptions filled by non-designated pharmacies would not have been captured in this sampling, potentially resulting in the false indication of a drug regimen change (i.e. change from combination therapy to mono-therapy).

It is also important to note that drug expenditures were calculated using AWP-10%. We selected this figure mainly to provide a common metric for assessing costs of hypoglycemic drug utilization. The dollar totals do not include the cost of syringes or blood glucose monitoring devices or supplies, or medications used for reasons and conditions other than blood glucose control.

Though various insurance types are represented, a majority of study patients were enrolled in a diabetes management program through one of two health

plans. Generalizability to other populations is impaired by a lack of knowledge of race and socio-economic status, and the absence of diagnostic information such as diabetes type and co-morbidities.

## CONCLUSION

Retail pharmacy data were used to describe hypoglycemic drug utilization and associated costs in a large population of ambulatory diabetic patients. Several important findings are reported here. First, sulfonylureas continue to be the mainstay of treatment in patients with type 2 diabetes. Second, many patients changed medication regimens during a 12-month period, not including changes in medication dosage. Third, patients 65 years of age and older were less frequently prescribed troglitazone, or metformin in mono-therapy, and were most frequently prescribed sulfonylureas as their only hypoglycemic agent. The difference in hypoglycemic drug type utilization among seniors was reflected in the average 12-month cost of hypoglycemic medications dispensed. For seniors, this cost was roughly 20% less than average hypoglycemic drug utilization costs for middle-aged and younger-aged diabetic patients.

Perhaps the recent attention directed towards tight glycemic control and enhanced control of post-prandial blood glucose will generate an increase in the use of combination drug therapies that includes newer hypoglycemic agents. However, though glycemic control may be enhanced through the use of some of the newer agents, there is no evidence to suggest that sulfonylureas are less effective than newer agents at preventing death and disability due to diabetes. In this population, sulfonylureas were by far the

most frequently used agents, particularly in older patients. Older patients were also less frequently dispensed prescriptions for troglitazone, and metformin in combination with a sulfonylurea. These findings may or may not suggest a difference in the standard of care delivered to seniors, but we believe it indicates a difference in the type of care received.

**Figure 1. Drug Regimen Categories**

| Regimen | |
|---|---|
| 1 | Insulin only |
| 2 | Insulin + troglitazone |
| 3 | Insulin + non-troglitazone agent |
| 4 | Sulfonylurea mono-therapy |
| 5 | Sulfonylurea + metformin |
| 6 | Sulfonylurea + non-metformin agent |
| 7 | Troglitazone mono-therapy |
| 8 | Glimepramide mono-therapy |
| 9 | Metformin mono-therapy |
| 10 | Other regimen not classified above |

**Table 1. Population Characteristics**

| | N | % |
|---|---|---|
| Total population | 2901 | |
| Age | | |
| Under 50 | 1002 | 34.5 |
| 50-64 | 1259 | 43.4 |
| 65 and older | 640 | 22.1 |
| Gender | | |
| Female | 1349 | 46.5 |
| Male | 1552 | 53.5 |
| Insurance type | | |
| Plan A | 967 | 33.3 |
| Plan B | 1562 | 53.8 |
| Other insurer | 250 | 8.6 |
| Cash | 122 | 4.2 |
| Insulin use | 890 | 30.7 |
| Oral hypoglycemic use | 2010 | 69.3 |

**Table 2a. Frequency and Percentage of Drug Regimens Utilized, Based Upon Dispensings During First 90 Days of the 12-Month Period**

| | Regimen | n | % |
|---|---|---|---|
| 1 | Insulin only | 723 | 24.92 |
| 2 | Insulin + Troglitazone | 91 | 3.14 |
| 3 | Insulin + non-troglitazone agent | 76 | 2.62 |
| 4 | Sulfonylurea mono-therapy | 1168 | 40.26 |
| 5 | Sulfonylurea + metformin | 404 | 13.93 |
| 6 | Sulfonylurea + non-metformin agent | 77 | 2.65 |
| 7 | Troglitazone mono-therapy | 34 | 1.17 |
| 8 | Glimepramide mono-therapy | 76 | 2.62 |
| 9 | Metformin mono-therapy | 202 | 6.96 |
| 10 | Other regimen not classified above | 50 | 1.72 |
| | TOTAL | 2901 | 100.00 |

**Table 2b. Comparison of Drug Regimen Utilization During First and Last 90 Days of the 12-Month Period.**

| Regimen | | First 90 days | | Last 90 days | | Change | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| 1 | Insulin only | 723 | 24.92 | 641 | 22.10 | -82 | 2.83 |
| 2 | Insulin + Troglitazone | 91 | 3.14 | 110 | 3.79 | +19 | 0.65 |
| 3 | Insulin + non-troglitazone | 76 | 2.62 | 87 | 3.76 | +11 | 1.14 |
| 4 | Sulfonylurea mono-therapy | 1168 | 40.26 | 914 | 31.51 | -254 | 8.76 |
| 5 | Sulfonylurea + metformin | 404 | 13.93 | 426 | 14.68 | +22 | 0.76 |
| 6 | Sulfonylurea + non-metformin | 77 | 2.65 | 179 | 6.17 | +102 | 3.52 |
| 7 | Troglitazone mono-therapy | 34 | 1.17 | 48 | 1.65 | +14 | 0.48 |
| 8 | Glimepramide mono-therapy | 76 | 2.62 | 66 | 2.28 | -10 | 0.34 |
| 9 | Metformin mono-therapy | 202 | 6.96 | 198 | 6.83 | -4 | 0.14 |
| 10 | Other regimen not classified | 50 | 1.72 | 232 | 8.00 | +182 | 6.27 |

## Table 3a. Frequency of Change in Hypoglycemic Drug Regimen Utilized During 12-Month Period

Patients remaining on same drug regimen or switching to different regimen during 12-month period

REGIMEN CATEGORY: LAST 90 DAYS

| REGIMEN CATEGORY: FIRST 90 DAYS | | N | Insulin only **1** | Insulin + Troglit-azone **2** | Insulin + non-troglit-azone **3** | Sulfon-ylurea mono-therapy **4** | Sulfon-ylurea + met-formin **5** | Sulfon-ylurea+ nonmet-formin **6** | Troglit-azone mono-therapy 7 | Glimep-ramide mono-therapy **8** | Metfor-min mono-therapy **9** | Other regimen not classified **10** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Insulin only | 723 | **593** | 39 | 35 | 2 | 1 | 2 | 4 | 0 | 4 | 43 |
| **2** | Insulin + Troglitazone | 91 | 15 | **51** | 11 | 0 | 0 | 2 | 3 | 1 | 0 | 8 |
| **3** | Insulin+ non-troglitazone | 76 | 19 | 13 | **23** | 7 | 2 | 8 | 0 | 1 | 0 | 3 |
| **4** | Sulfonylurea mono-therapy | 1168 | 4 | 3 | 7 | **869** | 121 | 58 | **11** | 2 | 24 | 69 |
| **5** | Sulfonylurea + metformin | 404 | 5 | 0 | 7 | 19 | **282** | 49 | 4 | 0 | 14 | 24 |
| **6** | Sulfonylurea + non-metformin | 77 | 2 | 0 | 0 | 9 | 3 | **50** | 1 | 2 | 1 | 9 |
| **7** | Troglitazone mono-therapy | 34 | 1 | 2 | 2 | 1 | 0 | 4 | **17** | 0 | 0 | 7 |
| **8** | Glimepramide mono-therapy | 76 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | **57** | 2 | 13 |
| **9** | Metformin mono-therapy | 202 | 1 | 0 | 1 | 5 | 14 | 1 | 5 | 2 | **151** | 22 |
| **10** | Other not classified | 50 | 1 | 2 | 1 | 1 | 3 | 3 | 2 | 1 | 2 | **34** |
| | Total | 2901 | 641 | 110 | 87 | 914 | 426 | 179 | 48 | 66 | 198 | 232 |

**Table 3b. Percent of Change in Hypoglycemic Drug Regimen Utilized During 12-Month Period**

Patients remaining on same drug regimen or switching to different regimen during 12-month period

| REGIMEN CATEGORY: FIRST 90 DAYS | N | REGIMEN CATEGORY: LAST 90 DAYS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Insulin only | Insulin + Troglit-azone | Insulin + non-troglit-azone | Sulfonyl-urea mono-therapy | Sulfonyl-urea + met-formin | Sulfonyl-urea+non metfor-min | Troglit-azone mono-therapy | Glimep-ramide mono-therapy | Metfor-min mono-therapy | Other regimen not classified |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1 Insulin only | 723 | **82%** | 5% | 5% | 0% | 0% | 0% | 1% | 0% | 1% | 6% |
| 2 Insulin + Troglitazone | 91 | 16% | **56%** | 12% | 0% | 0% | 2% | 3% | 1% | 0% | 9% |
| 3 Insulin+ non-troglitazone | 76 | 25% | 17% | **30%** | 9% | 3% | 11% | 0% | 1% | 0% | 4% |
| 4 Sulfonylurea mono-therapy | 1168 | 0% | 0% | 1% | **74%** | 10% | 5% | 1% | 0% | 2% | 6% |
| 5 Sulfonylurea + metformin | 404 | 1% | 0% | 2% | 5% | **70%** | 12% | 1% | 0% | 3% | 6% |
| 6 Sulfonylurea + non-metformin | 77 | 3% | 0% | 0% | 12% | 4% | **65%** | 1% | 3% | 1% | 12% |
| 7 Troglitazone mono-therapy | 34 | 3% | 6% | 6% | 3% | 0% | 12% | **50%** | 0% | 0% | 21% |
| 8 Glimepramide mono-therapy | 76 | 0% | 0% | 0% | 1% | 0% | 3% | 1% | **75%** | 3% | 17% |
| 9 Metformin mono-therapy | 202 | 0% | 0% | 0% | 2% | 7% | 0% | 2% | 1% | **75%** | 11% |
| 10 Other not classified | 50 | 2% | 4% | 2% | 2% | 6% | 6% | 4% | 2% | 4% | **68%** |

**Table 4. Percentage of Patients Prescribed Each Drug Regimen; Stratified By Gender**

| | REGIMEN CATEGORY | N | Female | Male | |
|---|---|---|---|---|---|
| **1** | Insulin only | 723 | 28.1% | 22.2% | p = 0.0002 |
| **2** | Insulin + Troglitazone | 91 | 3.9% | 2.5% | p = 0.0386 |
| **3** | Insulin + non-troglitazone agent | 76 | 2.4% | 2.8% | p = 0.4362 |
| **4** | Sulfonylurea mono-therapy | 1168 | 35.8% | 44.1% | p < 0.0001 |
| **5** | Sulfonylurea + metformin | 404 | 14.0% | 13.9% | p = 0.9029 |
| **6** | Sulfonylurea + non-metformin | 77 | 2.5% | 2.8% | p = 0.6758 |
| 7 | Troglitazone mono-therapy | 34 | 1.2% | 1.2% | p = 0.9477 |
| **8** | Glimepramide mono-therapy | 76 | 3.1% | 2.2% | p = 0.1207 |
| **9** | Metformin mono-therapy | 202 | 7.5% | 6.5% | p = 0.3013 |
| **10** | Other regimen | 50 | 1.5% | 1.8% | |
| | Total | 2901 | 100% | 100% | |

**Table 5a. Percentage of Patients Prescribed Each Drug Regimen; Stratified By Age**

| | | | AGE | | | |
|---|---|---|---|---|---|---|
| REGIMEN CATEGORY | | N | Under 50 | 50-64 | 65 or older | |
| **1** | Insulin only | 723 | 36.9% | 18.4% | 19.1% | p < 0.0001 |
| **2** | Insulin + Troglitazone | 91 | 4.1% | 3.3% | 1.4% | p = 0.0092 |
| **3** | Insulin + non-troglitazone agent | 76 | 2.4% | 2.5% | 3.1% | p = 0.6478 |
| 4 | Sulfonylurea mono-therapy | 1168 | 30.8% | 43.6% | 48.4% | p < 0.0001 |
| **5** | Sulfonylurea + metformin | 404 | 12.1% | 15.2% | 14.4% | p = 0.1004 |
| **6** | Sulfonylurea + non-metformin | 77 | 1.8% | 3.4% | 2.5% | p = 0.0568 |
| 7 | Troglitazone mono-therapy | 34 | 1.1% | 1.4% | 1.0% | p = 0.7058 |
| **8** | Glimepramide mono-therapy | 76 | 2.1% | 2.7% | 3.3% | p = 0.3315 |
| **9** | Metformin mono-therapy | 202 | 7.2% | 7.9% | 4.8% | p = 0.0476 |
| **10** | Other regimen | 50 | 1.5% | 1.9% | 2.0% | - |
| | Total | 2901 | 100% | 100% | 100% | |

**Table 5b. Percentage of Patients Prescribed Each Drug Regimen; Stratified By Age, Patients Under 40 Years of Age Excluded**

| | | | AGE | | | |
|---|---|---|---|---|---|---|
| | REGIMEN CATEGORY | n | 40-49 | 50-64 | 65 or older | |
| 1 | Insulin only | 723 | 20.1% | 18.4% | 19.1% | p = 0.6506 |
| 2 | Insulin + Troglitazone | 91 | 5.0% | 3.3% | 1.4% | p = 0.0013 |
| 3 | Insulin + non-troglitazone agent | 76 | 2.8% | 2.5% | 3.1% | p = 0.7627 |
| 4 | Sulfonylurea mono-therapy | 1168 | 39.6% | 43.6% | 48.4% | p = 0.0067 |
| 5 | Sulfonylurea + metformin | 404 | 15.6% | 15.2% | 14.4% | p = 0.8275 |
| 6 | Sulfonylurea + non-metformin | 77 | 2.4% | 3.4% | 2.5% | p = 0.3715 |
| 7 | Troglitazone mono-therapy | 34 | 1.0% | 1.4% | 1.0% | p = 0.6493 |
| 8 | Glimepramide mono-therapy | 76 | 2.8% | 2.7% | 3.3% | p = 0.7612 |
| 9 | Metformin mono-therapy | 202 | 9.1% | 7.9% | 4.8% | p = 0.0107 |
| 10 | Other regimen | 50 | 1.6% | 1.9% | 2.0% | - |
| | Total | 2901 | 100% | 100% | 100% | |

**Table 6. Percentage of Patients Prescribed Each Drug Regimen; Stratified By Insurance Type**

| | REGIMEN CATEGORY | N | Plan A | Plan B | Other Insurance | Cash | |
|---|---|---|---|---|---|---|---|
| 1 | Insulin only | 723 | 24.1% | 25.3% | 27.2% | 22.1% | p = 0.6444 |
| 2 | Insulin + Troglitazone | 91 | 3.8% | 3.1% | 2.0% | 0 | - * |
| 3 | Insulin + non-troglitazone agent | 76 | 3.4% | 2.1% | 2.8% | 3.3% | p = 0.2019 |
| 4 | Sulfonylurea mono-therapy | 1168 | 39.3% | 40.6% | 37.2% | 50.1% | p = 0.1010 |
| 5 | Sulfonylurea + metformin | 404 | 11.8% | 15.8% | 12.8% | 9.8% | p = 0.0187 |
| 6 | Sulfonylurea + non-metformin | 77 | 3.4% | 2.1% | 2.8% | 3.3% | p = 0.2477 |
| 7 | Troglitazone mono-therapy | 34 | 0.8% | 1.2% | 2.4% | 0.8% | - * |
| 8 | Glimepramide mono-therapy | 76 | 4.3% | 1.3% | 2.8% | 5.7% | p < 0.001 |
| 9 | Metformin mono-therapy | 202 | 6.5% | 4.0% | 8.4% | 2.5% | p = 0.0107 |
| 10 | Other regimen | 50 | 2.6% | 4.5% | 1.6% | 2.4% | - |
| | Total | 2901 | 100% | 100% | 100% | 100% | |

* $X^2$ not reported due to cells with less than 5 subjects

**Table 7. Prescriptions for Brand Name Sulfonylurea Products and Age, Gender, and Insurance Type**

| | n | Percentage of Patients Dispensed Brand Name Product | |
|---|---|---|---|
| Age | | | |
| under 50 | 430 | 54.2% | |
| 50-64 | 740 | 50.1% | |
| 65 and older | 402 | 48.3% | p = 0.2079 |
| Gender | | | |
| Female | 672 | 48.4% | |
| Male | 900 | 52.6% | p = 0.1000 |
| Insurance Type | | | |
| Plan A | 316 | 64.0% | |
| Plan B | 368 | 41.8% | |
| Other Insurance | 69 | 55.2% | |
| Cash | 45 | 64.6% | p < 0.001 |

**Table 8. Troglitazone Prescribing and Age Category**

| Age | N | Number prescribed troglitazone | % prescribed Troglitazone* |
|---|---|---|---|
| 40-49 | 616 | 125 | 20.3% |
| 50-64 | 1259 | 222 | 17.6% |
| 65 + | 640 | 65 | 10.2% |
| Total | 2515 | 412 | 16.4% |

*p < 0.0001

**Table 9. Prescriptions for Hypoglycemic Drugs: 12-Month Expenditure**

| | n | 12-month expenditure (mean) | Pr > F |
|---|---|---|---|
| Age | | | |
| under 50 | 1002 | $580.80 | |
| 50-64 | 1259 | $593.23 | |
| 65 and older | 640 | $470.38 | < 0.0001[a] |
| Gender | | | |
| Female | 1349 | $538.83 | |
| Male | 1552 | $531.72 | 0.1172[b] |
| Insurance Type | | | |
| Plan A | 967 | $521.63 | |
| Plan B | 1562 | $587.82 | |
| Other Insurance | 250 | $526.01 | |
| Cash | 122 | $385.37 | 0.0002[a] |

a. Analysis of Variance, Tukey's test
b. Student's t-test for independent samples

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**Changes in Oral Hypoglycemic Therapy: Influence of Nonadherence as Determined by Medication Possession**


## ABSTRACT

**Background** Recent large trials have provided evidence that intensive therapy for achieving tight glycemic control can reduce the risk of several types of diabetic complications. Tight glucose control necessarily presumes strict adherence to the prescribed hypoglycemic regimen. However, adherence to prescribed drug therapy for chronic diseases is known to be sub-optimal.

**Objective** To determine if nonadherence, as determined by medication possession, is associated with changes in hypoglycemic drug prescribing; either as a change in medication strength or a change in type of hypoglycemic medication dispensed.

**Methods** .A retrospective cohort study examining retail pharmacy dispensings of sulfonylureas and metformin. The medication possession ratio (MPR) was used to assess adherence, with patients that did not receive a sufficient quantity of medication to cover eight of ten days in the period (MPR < 8:10) classified as nonadherent. Outcomes assessed were change in strength of hypoglycemic medication dispensed and change in type of hypoglycemic medication dispensed. Multivariate logistic regression was used

to estimate the influence of medication possession on these outcomes, controlling for the potential confounding factors age, gender, insurance type, and the total number of all pharmacy dispensings.

**Results** For patients receiving dispensings only for a sulfonylurea, those failing to possess medication for eight of ten days (MPR < 8:10) were 41.7% more likely to receive a dispensing for a different strength of medication in subsequent months (OR 1.42, 95% CI 1.02 – 1.96). Such patients were also 47.1% more likely to receive a dispensing for a different strength or different type of hypoglycemic medication (OR 1.47, 95% CI 1.05 – 2.06). For the smaller sub-population of users of only metformin (n = 166), a statistically significant increase in the likelihood of either a change in strength or type of hypoglycemic drug dispensed was not found for those having an MPR less than 8:10. However, for the combined sample of patients receiving either monotherapy with a sulfonylurea or metformin, those having an MPR less than 8:10 were 36.4% more likely to receive a dispensing for a different strength of medication (OR 1.36, 95% CI 1.019 – 1.83), or for a different strength or type of hypoglycemic medication (OR 1.39, 95% CI 1.027 – 1.87).

**Conclusions** Glycemic control would expectedly be poorer among patients failing to possess prescribed hypoglycemic medication. In this study, patients failing to refill prescriptions when due were more likely to receive a dispensing for a different strength or type of hypoglycemic

medication in subsequent months. This finding suggests that for patients that do not tightly adhere to therapy, providers may respond to poor glucose control by increasing the amount of medication prescribed. This response may precipitate dangerous hypoglycemic reactions, and fails to address the root cause of poor glycemic control for such patients, potentially resulting in diabetic complications that could have been prevented.

## INTRODUCTION

Patients with diabetes are at risk for numerous adverse health outcomes. Beyond consequences immediately related to blood glucose regulation, such as hypoglycemia or ketoacidosis (1), diabetes increases risk for 'macro' vascular diseases such as myocardial infarction and stroke (2). Diabetics are also more likely to develop hypertension and dyslipidemia (3), which are risk factors for developing these outcomes. In addition to macrovascular diseases, diabetes also increases the risk of developing diseases resulting from damage to the smaller blood vessels, such as retinopathy, neuropathy, and nephropathy (4). The quality of life in patients with diabetes often diminishes over time as diabetic complications become disabling (5).

Appropriate management of diabetes can reduce and delay the sequelae of this disease. Therapeutic interventions have been proven effective in controlling blood glucose levels (6) and in the longer-term, preventing some types of diabetes complications (7-9). Dietary changes and routine exercise are fundamental interventions. Often, however, normalization of blood glucose control can only be achieved through drug treatment (10).

In addition to resolving blood glucose instability in many patients, drug therapy has been demonstrated to confer the added benefit of preventing some types of diabetes complications. Results from two large trials have provided

evidence that drug therapy can reduce the incidence of micro-vascular disease in patients that are aggressively managed.

Researchers in the Diabetes Control and Complications Trial (DCCT) (9) compared standard care with intensive drug treatment and monitoring regimens in 1,441 type 1 diabetics during a ten-year period. In this study, the risk of developing retinopathy, nephropathy, and neuropathy was reduced by 76%, 50%, and 60% respectively among diabetics receiving the intense treatment. This finding led researchers to conclude that intensive drug therapy "delays the onset and slows the progression" of these diseases.

The United Kingdom Prospective Diabetes Study (UKPDS) (7) investigated whether intensive drug therapy reduced the incidence of diabetic complications in type 2 diabetes. In this study, 3867 patients with newly diagnosed disease were followed during a 10-year period. As in the DCCT, researchers attempted to determine if intense treatment and monitoring would reduce the incidence of diabetic complications. The results of the UKPDS provided compelling evidence that drug therapy can reduce the incidence of certain types of complications in patients with type 2 disease. Compared with patients treated with conventional care, the risk for developing microvascular complications in patients receiving intensive therapy was reduced by 25%. Further, the risk of developing retinopathy was reduced by 21%, while the risk of developing microalbuminurea was reduced by 34%. The incidence of

myocardial infarction was also lesser in the group treated intensively, though the 16% difference observed between groups failed to achieve statistical significance ($p = 0.052$).

These two trials provided strong evidence that tight control of blood glucose can prevent the microvascular complications in patients with diabetes, and may reduce the risk for macrovascular complications such as myocardial infarction. Since the publication of these trials, standards for the treatment of diabetes have incorporated tight blood glucose control as an objective of therapy. Thus, drug treatment is aimed at maintaining normal blood glucose throughout the day to obtain the benefits described in these trials.

Patient adherence to prescribed drug regimens is implicit to a strategy of tight blood glucose control. When medications are not taken according to instructions, optimal control of blood glucose will clearly be compromised. This may be the case for many diabetic patients. Patient adherence with prescribed medication regimens for chronic diseases is known to be sub-optimal (11-13) (14), and patients with diabetes in particular are known to have difficulty adhering to prescribed dietary, exercise, and drug therapies (15, 16). Further complicating matters is the progressive nature of diabetes, as patients generally experience a worsening of glycemic control over time. Therefore, not only is adherence important in reducing the risk of diabetic complications,

it is a fundamental component of active participation in therapy that continually requires assessment of medication needs for sustaining glucose control.

Thus, both disease progression and poor adherence can cause inadequate blood glucose control, and it is important to distinguish between the two. The patient who is poorly controlled because his disease has progressed potentially requires a different intervention than the patient who is poorly controlled due to poor adherence. Increasing the dose of medication for the patient in the latter scenario may result in a dangerous hypoglycemic reaction.

Our working hypothesis was that patients that do not adhere to prescribed drug regimens are more likely to be poorly controlled; and such poor control will be manifested as a change in medication dose or a change in medication prescribed. To investigate this hypothesis, we assessed adherence with sulfonylurea or metformin therapy using pharmacy claims data. We determined whether patients that were nonadherent to prescribed therapy were more likely to receive a change in dose or change in hypoglycemic drug dispensed during subsequent months.

## METHODS

### Identification of the study samples

We conducted a retrospective cohort study using prescription dispensing information. Consumer Value Stores, Inc (CVS) provided pharmacy utilization data used in this study. The data included over one-quarter million dispensings to 5056 diabetic patients between April 1997 and May 1999. Most patients included in this population were enrollees of one of two area health plans, and participants in a special managed care program in diabetes through these plans. Patients were restricted to designated CVS pharmacies for pharmacy services. The data provided represented pharmacy utilization by patients enrolled in these two health plans from the designated pharmacies. The restriction to designated pharmacies was an advantageous feature, potentially resulting in a more complete representation of pharmacy utilization.

Of the patients included in the total population, we identified those that received any hypoglycemic medication during a 12-month observation period. From this population, we identified patients receiving mono-therapy with a sulfonylurea or mono-therapy with metformin during the first four months of this 12-month period. Patients who received two or more different types of hypoglycemic medication during this four-month period were excluded. Thus, two samples were created: patients receiving monotherapy with sulfonylurea and patients receiving monotherapy with metformin.

Patients who did not receive the same strength of medication and same number of tablets per day for all dispensings during the four-month period were excluded from study. Thus, the two samples represented patients receiving dispensings for either only a sulfonylurea or only metformin at the same dose during the four-month period, and receiving at least one dispensing of a hypoglycemic medication during the following eight months.

**Determining change in dose or medication regimen**

We assessed the influence of adherence for two main outcomes: change in dose of sulfonylurea or metformin; or change in hypoglycemic drug dispensed. To determine change in dose, we compared the initial strength of medication with additional subsequent dispensings during the following eight months. Also, we identified patients receiving an increased quantity of the same strength of medication (e.g. two tablets daily instead of one). To identify such patients, we compared the number of tablets in the daily dose for all dispensings. By dividing the quantity supplied by the days supply of medication received, we were able to determine the number of tables prescribed per day. Patients who received a different strength of a same medication, or who were prescribed a different number of tablets per day during the eight months following the four-month period were classified as having a change in dose of sulfonylurea or metformin.

In addition to change in medication dose, we identified patients who received a dispensing for a different type of hypoglycemic drug in the months following the initial four-month period. The two outcomes were also used to create a combined outcome of receiving a dispensing for either a different strength or type of hypoglycemic medication.

**Calculating the medication possession ratio**

We used the medication possession ratio (MPR) as the measure of adherence with prescribed hypoglycemic drug therapy. The MPR describes the number of days that a patient was in possession of medication (17). To calculate the MPR, we determined the total days supply of medication received for all dispensings preceding the last dispensing of the four-month period. A ratio was created using the days supply of medication received and the number of days between the first and last dispensing during the four-month period. For example, the MPR for a patient that received three dispensings of 30 tablets each (90 tablets) during a period of 113 days would be 90:113, or roughly 8:10. For the purposes of this research, medication possession for at least 80% of days (MPR $\geq$8:10) was considered to be adherent. Other researchers have used this threshold in studies of adherence to therapies for other chronic conditions, such as hormone-replacement therapy (18); hypertension (19, 20); and depression (21). Patients who received only one dispensing during the four-month period but who received medication in following months were classified as non-adherent.

A limitation of the MPR as used to assess adherence is the potential for misclassification, since a patient may possess but not consume a medication. Possession of medication has however, been considered a useful 'first-order' measure of adherence (22), since patients must first possess medication before they can adhere to therapy

**Potential confounding variables**

We also examined the effect of four other factors on change in dose of hypoglycemic medication or change in type of hypoglycemic medication prescribed. One such factor, the number of medications prescribed, was thought to potentially be an important influence on medication possession and change in hypoglycemic therapy. To approximate the number of medications prescribed, we identified the total number of dispensings for any class of medication during the four-month period; including medications for conditions other than diabetes. Three categories of this variable were created: less than 5 dispensings, 5-15 dispensings, or more than 15 dispensings. We also assessed the effect of patient age, and categorized this variable using categories of less than 50 years of age, 50-65 years, and greater than 65 years of age. Stratifications for the total number of prescriptions dispensed and patient age were based upon assessment of parametric form, as described in the following section.

The type of insurance used for prescription reimbursement was also included as a potential confounder. We categorized insurance type as health plan A, health plan B, or a third category that included all other insurance types and cash. We also included gender as an additional potential confounding variable.

Based on the methodology for variable identification described above and as presented in figure 2, we determined the relative risk of a change in medication dose, change in class of hypoglycemic medication prescribed, or a combined outcome of either for patients having a medication possession ratio less than 8:10, as compared to those having an MPR ≥8:10. Additionally, we assessed the influence of four other variables: the total number of prescriptions dispensed, age category, insurance type, and gender; attempting to control for the effect of these variables where necessary.

**Statistical methods**

Univariate statistics were used to describe the frequency and percent of monotherapy with a sulfonylurea or metformin. For each of the two samples, we categorized patients by gender, age, insurance type, and the total number of prescriptions dispensed. These characteristics were also presented as frequencies and percentages. We also determined the frequency and percent

of subjects having an MPR greater than 8:10 and 9:10. For all analyses involving the MPR, we used the lower threshold of ≥8:10.

We assessed the parametric form of the two continuous variables: age and total number of prescriptions dispensed. This was accomplished by logistically modeling quartiles of the frequency distribution to assess linearity. For each independent variable, models were created for each quartile of the variable's frequency distribution and each dependent variable. The resulting parameter estimates were exponentiated and plotted to determine if a linear trend was present. Non-linear relationships suggested the need for stratification of each continuous variable for inclusion in multivariate logistic models.

Bivariate analyses were used to assess the relationship between the MPR and other independent variables, and between independent and dependent variables. Chi square analyses were used to assess the relation between the medication possession ratio and the potential confounding variables. We also used chi-square analyses to examine the relation between all independent variables and the outcomes of change in dose and change in medication dispensed. For each independent variable, bivariate logistic regression was used to determine the relation between variable and change in dose and change in medication dispensed. These results were presented as an odds ratio with 95% confidence intervals.

Multivariate statistics were used to identify the presence of collinearity between independent variables, to determine the presence of interactions between independent variables, and to assess the influence of the MPR on outcome variables when other potential confounding variables were included.

Collinearity diagnostics were performed using the PROC REG procedure for multiple regression as suggested by Allison (23). Collinearity was assessed for all independent variables in separate models with dependent variables change in dose, change in medication dispensed, and the combined outcome of change in either. Presence of collinearity was determined using thresholds for condition index and proportion of variance shared as described by Tabachnick and Fidell (24).

Test for interaction between variables was performed using the chunk test for multivariate logistic models as described by Kleinbaum (25). For this procedure, we calculated the difference in the –2log statistic between full and reduced models. Full models included all possible interaction and single terms: Reduced models included single terms (variables) only. The difference in –2log statistic between full and reduced models was tested for significance using the Chi-square distribution, with degrees of freedom equal to the difference in terms between the two models. A difference in –2log value that was less than the $X^2$ statistic indicated that an interaction was not present.

Final multivariate logistic models contained only variables with significant terms, or a significant strata. Initial models contained all independent variables. Least significant terms were removed in order (backward elimination), observing the effect of change in the parameter estimate beta and confidence interval for each variable eliminated. Terms were excluded from the model if they were non-significant contributors and if their removal resulted in small or no change in the parameter estimate for the MPR. In models where it was not a significant influence on the outcome variable, the MPR variable was removed from the model, and the influence of other significant terms was assessed.

## RESULTS

Table 1 presents the gender, age category, insurance type, and total number of prescriptions dispensed for patients in the sulfonylurea and metformin samples. Nearly six times as many patients received sulfonylurea monotherapy than metformin monotherapy (967 versus 166). Also, a greater percentage of males received sulfonylurea monotherapy, yet the percent of males and females that received monotherapy with metformin was similar. The age stratifications presented reflect the parametric form of this variable. Nearly half of all patients in both samples were between 50-65 years of age. A notable disparity was the higher percentage of patients in youngest age strata among metformin users, as compared with subjects in the sulfonylurea sample. Conversely, the sulfonylurea sample included a greater percentage of patients 65 years of age or older as compared with the metformin sample.

In both the sulfonylurea and metformin samples, nearly 90% of patients were covered by one of the two predominant insurance plans. The remainder of patients used other insurance plans for prescription payment, or paid cash. Percentages of categories of insurance type were similar for the sulfonylurea and metformin samples.

More than half of patients were categorized as receiving a total of 5-15 prescriptions during the four-month period, a strata that represented the

second and third quartiles of the distribution of this variable. We chose to combine these quartiles due to a similar relationship between each quartile and the outcome variables. However, the first and fourth quartile of the frequency distribution of this variable differed from the second and third quartile in relation to the dependent variables, necessitating the three levels created.

Table 2 presents the results of univariate analysis of the medication possession ratio. The percentage of patients possessing medication for at least 80% of days during the time period was 77.2% and 71.1% for the sulfonylurea and metformin samples respectively. The percentage of patients possessing medication for at least 90% of days was 66.8% for the sulfonylurea monotherapy sample, and 56.6% for those dispensed only metformin. The average percentage of days medication was possessed was similar (91% for patients receiving only sulfonylurea; 86.6% for patients receiving only metformin). This percentage is highly skewed, with some patients receiving quantities of medication that were greater than the quantity required to cover 100% of days between dispensings.

Table 3 presents the relation between the potential confounding variables and the medication possession ratio. The percentage of patients having an MPR < 8:10 did not differ significantly by gender or insurance type among patients receiving either dispensings for a sulfonylurea or metformin. Among

sulfonylurea users, patients in the youngest age category were more frequently identified as having an MPR less than 8:10 (age under 50: 33.19%; age 50-64: 19.46%; Age 65+: 15.59%; $p < 0.01$). Similar percentage distributions were observed for metformin users, though the ability to detect a statistically significant difference was likely influenced by the smaller number of patients in this sample. Patients receiving less than five total dispensings during the first four months of the 12-month period were also more frequently categorized as having an MPR less than 8:10. Subjects receiving greater than 15 dispensings were least frequently categorized as having an MPR < 8:10. These differences were statistically significant among patients in the sulfonylurea sample ($p < 0.01$).

Tables 4a and 4b present the comparisons of proportions of patients having an MPR < 8:10 and the potential confounding variables with change of dose, change in medication dispensed, or the combined outcome of either. More than twice as many patients were identified as having a change in dose of hypoglycemic medication as compared with a change in type of drug dispensed (Sulfonylurea sample: change in dose: 58.53%, change in regimen: 26.78%, Metformin sample: change in dose: 48.19%; change in drug dispensed: 18.07%).

Males and females in the sulfonylurea group were roughly equally likely to experience a change in dose or change in drug dispensed, though the

percentage of metformin patients that experienced a change in drug was non-significantly higher among males (change in dose: sulfonylurea, males versus females: 59.01% v 59.35%; change in dose: metformin, males versus females: 53.75% v 48.84%. change in drug: sulfonylurea, males versus females: 25.70% v 28.35%; change in drug: metformin, males versus females: 22.35% v 13.58%). In both the sulfonylurea and metformin samples, younger patients were more frequently identified as having a change in dose or drug dispensed (change in sulfonylurea dose, age less than 50 versus age 65 years or older: 65.94% v 52.36%; change in metformin dose, age less than 50 versus age 65 years or older: 54.55% v 40.00%; change in drug among sulfonylurea users, age less than 50 versus age 65 years or older: 29.26% v 17.57%; change in drug among metformin users, age less than 50 versus age 65 years or older: 23.64% v 20.00%). These differences were only statistically significant in the sulfonylurea sample ($p < 0.01$). No statistically significant differences were observed between changes in medication dose or regimen and health plan or number of prescription dispensings. Patients in both samples having an MPR of less than 8:10 experienced a dose change more frequently (sulfonylurea: MPR < 8:10: 25.62%; MPR ≥8:10: 18.70%, metformin: MPR < 8:10: 32.50%, MPR ≥8:10: 25.58%) This difference between values for MPR < 8:10 and MPR ≥8:10 was nearly equal for both the sulfonylurea and metformin groups. However, the difference between groups was only statistically significant in the sulfonylurea group ($p < 0.05$), likely reflecting the fewer number of patients in the metformin sample. The proportion of patients having an MPR < 8:10 did

not differ significantly among those with a change in hypoglycemic drug dispensed for each sample (sulfonylurea: MPR < 8:10: 23.55%; MPR ≥8:10: 22.46%, metformin: MPR < 8:10: 30.00%, MPR ≥8:10: 28.68).

Bivariate and multivariate logistic regression models were also used to examine the relation between independent and dependent variables. These results are presented for the sulfonylurea and metformin samples, in analyses of the relation between each variable and the outcomes of change in medication dose (tables 5a, 5b) or change in drug dispensed (tables 6a, 6b). For the sulfonylurea sample, patients experiencing a change of dose were 50% more likely to be categorized as having an MPR < 8:10 (OR 1.50; 95% CI 1.09 – 2.05, p = 0.0118). The MPR was not statistically significantly associated with a change in medication dispensed among sulfonylurea users, or with a change of dose or medication dispensed among metformin users. Sulfonylurea patients 65 years of age and older were 43% less likely to experience a dose change (OR 0.57, 95% CI 0.40 – 0.81, p = 0.0018). Male gender, insurance type, and the total number of dispensings were not found to be significant influences on change in dose or of change in drug dispensed in either sample.

**Multivariate results**

We assessed the influence of the MPR on three outcomes: change in dose, change in drug dispensed, and the combined outcome of change in dose or drug dispensed. We examined the effect of MPR on these outcomes for three populations: patients dispensed sulfonylureas, patients dispensed metformin, and a combined sample of patients dispensed either monotherapy with a sulfonylurea or monotherapy with metformin. In sum, nine multivariate models were created to assess these relationships.

For each of these nine models, we assessed collinearity and interaction between variables. Collinearity between independent variables was not detected at condition indices above the threshold of 30. However, collinearity diagnostics indicated a high degree of shared variance between the number of prescriptions dispensed and age. Interaction between the MPR and other independent variables was assessed using the chunk test described by Kleinbaum. We did not detect a significant interaction between any combination of independent variables, as determined by comparing the difference in –2log statistic between full and reduced models with a chi-square value. These results are presented in table 7.

Tables 8a-c, 9a-c, and 10a-c present the multivariate results of the nine models. In these tables we have presented the results of models that include all independent variables in the logistic regression, followed by a final model

containing only significant terms. For models having no significant terms, only the model containing all independent variables is presented.

Tables 8a, 8b, and 8c present the multivariate results from the sulfonylurea sample for outcomes of change in dose, change in medication dispensed, and the combined outcome of change in dose, respectively. Table 8a presents the results for the outcome of change in dose. In a model containing all independent variables, the risk associated with a dose change was 42% greater among those having an MPR < 8:10. We removed from this model the non-significant terms gender, insurance type, and total number of dispensings. The resulting final model included only age and MPR < 8:10. Based on this model, patients that were 65 years of age or older were significantly less likely to experience a change in dose of sulfonylurea (OR 0.60; 95% CI 0.41 – 0.85). Age was also a significant influence in models for the outcome of change in medication dispensed in the sulfonylurea sample. Patients 65 years of age or older were less likely to be included among those with a change in type of medication dispensed (OR 0.51; 95% CI 0.34 – 0.78). Neither the MPR nor any other independent variable was significantly associated with a change in drug dispensed in the sulfonylurea sample.

Outcomes were combined to create a category of patients that included patients having either a change in dose or change in medication dispensed. For this combined outcome, the MPR and older age were both associated with

the risk of change in dose or medication dispensed; with MPR < 8:10 increasing the risk of this outcome by 50% (OR 1.50; 95% CI 1.08 – 2.08) and an age of 65 years or greater decreasing the risk of this outcome by 38% (OR 0.62; 95% CI 0.43 – 0.89).

Based upon the results of the multivariate logistic models for the metformin sample (Tables 9a-c), none of the independent variables was a significant influence of change in dose, change in medication dispensed, or the combined outcome of either. The lack of significant predictors in the metformin sample was potentially a result of sample size. We created a third sample of patients by combining the sulfonylurea and metformin populations. As in the models for the sulfonylurea sample, the MPR and age 65 years or older were significant influences of change in medication dose in the sample of combined patients (MPR < 8:10: OR 1.38; 95% CI 1.04 – 1.84, Age 65 or older OR 0.62, 95% CI 0.45 – 0.87). The oldest age group was the only variable with statistically significant influence in the model for change in medication dispensed in the combined sample (OR 0.55; 95% CI 0.38 – 0.81). Last, using a population that included both the sulfonylurea and metformin samples, the MPR and older age were significantly associated with the combined outcome of change in dose or change in medication dispensed. The results of models using the combined sample of patients are presented in tables 10a-c.

## DISCUSSION

Adherence to prescribed drug regimens is a common problem in patients with chronic diseases. Adherence to prescribed drug regimens in patients with diabetes is particularly important, since tight control of blood glucose has been demonstrated to reduce the incidence of many types of diabetes complications. Nevertheless, non-adherence to hypoglycemic therapy has been identified as a major barrier to effective management of diabetes. Lack of adherence with prescribed hypoglycemic medications has been correlated with diminished blood glucose control (26-28), which in turn can result in adverse health outcomes, both in the long and short-term.

Much research has been conducted investigating the cause for lack of adherence to drug therapy. Immediate barriers to adherence include the cost of medication, access to medication, and the complexity of the drug regimen. Beyond these barriers, determinants of adherence are more complex, and include physiologic, cognitive, behavioral, and environmental factors (29). For example, the health belief model has been reported to predict adherence to drug therapy (30).

According to the health belief model, adherence will be improved when patients perceive their disease to pose a threat to their health, and believe that prescribed medications will be effective in decreasing the risk of morbidity. In one study, knowledge about hypoglycemic medications among diabetic

patients in the UK was found to be poor, with only 35% of patients recalling receiving any information about their hypoglycemic medication (31). One in five patients surveyed in this study reported missing at least one dose of their hypoglycemic medication per week. The lack of knowledge of hypoglycemic drug therapy was perhaps a contributing factor resulting in the poor adherence rates observed, according to the principles of the health belief model.

Other explanatory paradigms for predicting and understanding the behavior of adherence include self-efficacy theory (32), the transtheoretical (stages of change) model (33), and social learning theory (34). Each of these involves patients taking active control of the disease management process, including understanding the need for adherence to recommended therapies.

Lack of adherence to hypoglycemic medications is a recognized, though perhaps under-appreciated problem. For example, Ward found that physicians may tend to over-estimate patients' adherence to prescribed medications (35). Yet the evidence continues to accumulate. Numerous studies of various methodology have demonstrated that drug treatments for chronic conditions are often not taken as prescribed (36, 37). Clearly this is an area of pharmacotherapy that deserves heightened focus.

In this study, we attempted to demonstrate that lack of adherence to prescribed hypoglycemic medication increases the likelihood that prescribed

therapies will change. We assumed that a change in medication dosage or a change drug type was an action in response to poor blood glucose control. Appropriate interventions for patients who are non-adherent to therapy would logically involve efforts intended to improve adherence. Increasing the amount of medication prescribed to a non-adherent diabetic patient is a potentially inappropriate intervention. Such a response may also be dangerous, resulting in increased risk of hypoglycemia (38) and longer-term complications resulting from continued poor glucose control.

In this study, the medication possession ratio was used to assess adherence. Also included in analyses were four other factors that were considered to be possibly associated with the MPR or related to the outcomes of change in medication dose or change in type of hypoglycemic medication dispensed. The age and gender of the patient were two of these factors. According to various studies, the relation between adherence and these two factors is unclear. For example, some studies have shown age and gender to be influences on adherence (39-40), though others have not (41-42). In one study of adherence with sulfonylurea therapy, age and gender were found to be statistically significant influences on drug regimen adherence (43) . In our study, we also included insurance type as a potential factor of influence. Though we had no knowledge of details regarding co-payment structures or formulary systems, we thought that attributes of the benefit design may have had an impact on adherence or change in dose or type of drug dispensed. The

total number of medications dispensed was the fourth of the other independent variables included in our study. We included this factor based upon research suggesting that adherence may be associated with the number of medications prescribed.

As determined by the medication possession ratio, adherence to drug therapy was poor among patients in both the sulfonylurea and metformin samples. Only 77% of patients in the sulfonylurea sample possessed enough mediation to cover at least 8 of 10 days during the four-month period. The percentage of patients receiving enough of their sulfonylurea medication to cover 9 of 10 days in the period was 67%. In the metformin sample, a lower percentage of patients possessed medication for each threshold. Of these patients, 71% received enough metformin to cover at least 8 of 10 days in the period, and 57% of patients possessed medication for 9 of 10 days. In summary, roughly one in four patients dispensed sulfonylureas did not possess enough medication to cover eighty percent of days during the four month period; and approximately one in three did not receive enough medication for ninety percent of days. Those receiving metformin monotherapy were less frequently in possession of medication.

The finding that patients do not regularly obtain hypoglycemic medication is not unexpected. In their investigation of compliance with sulfonylureas during a two-year time period, Venturini et al (44) reported a mean compliance rate of

83%: On average, patients did not possess medication for nearly one in five days. In a study using Medicaid pharmacy data, Sclar et al (43) found adherence with sulfonylurea therapy to be very low, with only 39% of patients receiving at least a six-month supply of medication during a period of 12 or more months.

Of the four potential confounding variables used in this study, only age and the total number of dispensings were significantly associated with the MPR. The percentage of patients having an MPR < 8:10 did not differ statistically significantly by gender or insurance type. Patients 65 years of age and older were more frequently in possession of medication for greater than 80% of days; patients under 50 years of age were least frequently is possession of medication for at least 80% of days. This difference was not statistically significant in the metformin sample, though sample size may have affected the ability to detect a significant difference. The finding that older patients were more frequently categorized as adherent may perhaps be explained as a greater concern among older patients for the protection of health, with a corresponding adherence with prescribed medications.

It was interesting that a greater number of prescriptions dispensed was more frequently associated with possession of medication for at least 80% of days. This finding may also be related to concerns for maintaining heath. Patients

receiving more medications are presumably less healthy, and perhaps more likely to take medications as prescribed.

**Multivariate analyses: Change in dose of hypoglycemic medication**

A change in dose of sulfonylurea or metformin was more than twice as frequently observed than a change in type of hypoglycemic medication dispensed. Diabetes is a progressive disorder, and even patients that adhere to therapy will require increased amounts of medication over time. In both the sulfonylurea and metformin samples, the youngest of the three age groups most frequently changed dose or type of drug dispensed, and the oldest age group least frequently experienced a change dose or type of drug dispensed. A possible explanation for the less frequent changes in drug dose among in older patients is that perhaps these patients are receiving a maximum dose of medication, a result of having diabetes for a longer duration. Betz-Brown et al. found that prescribers may tend to continue sulfonylurea therapies despite evidence that these agents are failing (45). The less frequent change in type of drug prescribed among older patients may be the result of avoidance of newer medications in older patients. For instance, troglitazone may have been avoided in older patients due to concerns of increased risk of hepatic toxicity in such patients. Another possible explanation for the more frequent changes in dose or type of drug dispensed in younger diabetics is increased attention to

achieving tight glucose control in younger patients, since these patients have a greater number of years in which to develop diabetic complications.

Both in bivariate and multivariate analyses that included other potential confounding variables, an MPR < 8:10 was found to be an influence on the outcomes of change of sulfonylurea dose. An MPR < 8:10 increased the risk of experiencing a change in dose by 50% in a bivariate model, and by 43% when controlling for patient age. Of patients in the metformin sample, those having an MPR < 8:10 were 40% more likely to experience a change in medication dose. However, this finding was not statistically significant, perhaps due to the smaller number of patients in this sample. Using a population that included patients from both the sulfonylurea and metformin samples, multivariate analyses demonstrated that an MPR < 8:10 was associated with an increased risk for experiencing a change in medication dose (OR 1.36; 95% CI 1.02 – 1.83).

Of all patients included in this study, those who did not possess enough medication to be adherent for at least 80% of days were 36% more likely to be prescribed an increased amount of medication. This percentage increased to 43% in analyses that included only those prescribed sulfonylurea monotherapy. The implications of this finding are uncertain. However, it is likely that the prescribing of a greater amount of sulfonylurea drug may place poorly adherent patients at an increased risk for hypoglycemic events.

Perhaps most importantly, a change in dose of hypoglycemic medication cannot be expected to induce an improvement in blood glucose control in patients that are non-adherent. Such patients may likely continue to be poorly controlled, and be at greater risk for diabetic complications.

**Multivariate analyses: Change in type of hypoglycemic medication dispensed**

Among patients in the sulfonylurea sample, only age was found to be significantly associated with experiencing a change in medication dispensed. Patients 65 years of age and older were 48% less likely to receive a different type of hypoglycemic medication than those under 50 years of age. In the metformin sample, age was not a significant influence on experiencing a change in type of drug dispensed. We examined the effect of age in a population that included patients from both the sulfonylurea and metformin samples. In this population, older age was again found to be an influence on change in type of drug dispensed. Patients 65 years of age or older were 45% less likely to experience a change in type of medication dispensed. The lesser frequency of change in type of medication dispensed among older patients may reflect an increased prevalence of co-morbidities within this age group. For example, many patients experiencing secondary failure of sulfonylurea therapy can regain blood glucose control through the addition of metformin. However, metformin is contraindicated in patients with heart failure or renal

disease. Additionally, patients with hepatic dysfunction would not be appropriate candidates for troglitazone therapy; which was commonly prescribed during the study period.

For the combined population that included those in the sulfonylurea and metformin samples, we also conducted multivariate analyses assessing the influence of the MPR on the combined outcome of either a change in dose or change in type of medication dispensed. In these models, an MPR < 8:10 was found to be of significant influence, increasing the risk of the combined outcome by 41% in a model that controlled for age. However, this result should be interpreted with caution. Though an MPR < 8:10 increased risk for a change in dose or change in type of drug dispensed, a direct influence of the MPR on change in type of drug dispensed was not detected in separate analyses. Thus, the influence of the MPR on the combined outcome appears to be largely due to the relation between the MPR and the outcome of change in dose.

We did not find gender, insurance type, or the total number of prescriptions dispensed to be associated with change in dose, change in drug dispensed, or a combined outcome of either change in dose or change in drug dispensed. Thus, we did not include these factors in final multivariate logistic models.

This study was conducted solely through the use of pharmacy claims data. Such data is useful for assessing adherence with drug therapy (46), though the use of multiple pharmacies may contribute to misclassification when dispensings of medication are not captured. An advantageous feature of these data was that patients were assigned to the pharmacies from which the data was generated. Thus, misclassification of non-adherence may have been minimized since patients were not reimbursed for prescriptions dispensed by other pharmacies. The large number of records available for review is also a strength of this study. We identified 967 patients receiving therapy with a sulfonylurea which were eligible for inclusion for study. Though the number of patients receiving metformin monotherapy was less, we felt it useful to include this population for comparison with the sulfonylurea group, since this drug is also frequently prescribed.

There were several important limitations to this study. Perhaps most importantly, this study evaluated a small number of potential influences of a change in dose or change in type of hypoglycemic medication dispensed. The factor of interest was medication possession, which has been used by various researchers to classify adherence. However, medication possession is only one of several potential determinants of medication adherence. Patients may possess medications yet take them incorrectly or sporadically. Certainly however, patients must possess medication in order to take them as prescribed. Thus, the medication possession ratio represents a potentially

useful 'first order' measure of medication adherence. However, the impact of various behavioral, clinical, social, and demographic factors on adherence was not assessed.

The method used for determination of the medication possession ratio may have also been a limitation. We chose to limit the sample to patients that had received at least 12 months of hypoglycemic therapy. To allow sufficient time to determine if a dose of medication changed or a new type of drug was prescribed following a period of stability, we used only a four-month period to calculate the MPR. It is possible that a longer period would have resulted in a different percent of patients classified as having an MPR < 8:10; and such difference may have generated different results. Adherence assessments in diabetes have used longer periods than we have used in this study (22, 43, 44). Additionally, a minimum MPR threshold of 8:10 may have been to low for classifying adherence in this population. A higher threshold may have been more appropriate in consideration of the degree of adherence necessary to achieve tight glycemic control.

Also, we may have been incorrect in our assumption that a change in dose or a change in type of medication dispensed reflected unstable glucose control. For instance, some patients identified as experiencing a change in dose of hypoglycemic medication may have been new diabetics being titrated to their medication. Also, factors such as allergies or intolerances may have been a

cause for change in medication type dispensed, and not necessarily poor blood glucose control. However, it seems improbable that new diabetics accounted for the majority of the 59% of patients in the sulfonylurea sample and the 48% of patients in the metformin sample that were identified as having a change in dose. Likewise, allergy or intolerance to a medication would presumably not account for the majority of the 27% of sulfonylurea users that were dispensed a different type of hypoglycemic medication, especially given the high degree of tolerance ascribed to sulfonylureas (47). However, metformin may cause side effects such as abdominal discomfort and diarrhea in as many as 30% of patients (48). It is possible that a proportion of metformin users who received a different type hypoglycemic medication were intolerant of metformin, and not necessarily poorly controlled. However, the number of such patients is likely to be small, since metformin intolerance usually appears early in therapy. Study patients received at least four months of therapy without a change in dose or drug.

The lack of availability of other data sources was also limiting. Medical data would have been useful for categorizing disease severity and duration, and for identifying relevant co-morbidities. For example, medical information would have been of use in determining if duration of disease was a contributing factor to the difference in frequency of dose change and change in type of drug dispensed among age groups. Laboratory data would have been useful in determining blood glucose control and its correlation with adherence to drug

therapy. Such information could have been used to validate the conceptual model presented in Figure 1. Last, information regarding prescription co-payment would have been of use, given evidence that acquisition costs affect medication purchase.

Despite these limitations, we feel that this study provides evidence to support the hypothesis that poor adherence leads to greater instability; in this case manifested as a change in medication dosage, or in the combined outcome of change in medication dose or type of medication dispensed.

Lack of adherence to prescribed drug therapy is an acknowledged problem. This problem can be complicated by a patient's lack of awareness of an adherence problem, or a lack of truthfulness in describing medication-taking behavior to the physician (49). The result of poor adherence with therapies for controlling blood glucose can have adverse consequences. Prescribers that increase the amount of medication prescribed to a poorly adherent diabetic patient may cause great risk of inducing dangerous hypoglycemic reactions. Further, the incidence of microvascular, and perhaps macrovascular complications will be increased in patients with adherence problems and corresponding poor glucose control.

## CONCLUSION

Non-adherence with prescribed sulfonylurea regimens, as measured by possession of medication less than 80 percent of days, increases the likelihood that prescribed hypoglycemic therapy will be changed by 43 to 50%. Such change in therapy, presumably a response to poor blood glucose control, fails to address the underlying cause of poor glucose control, and may potentially cause dangerous hypoglycemic reactions. Increased awareness of non-adherence with prescribed medications as a cause of inadequate blood glucose control is necessary. Further, interventions aimed at improving adherence should be increasingly examined as a potential effective means to improve diabetes care.

**Figure 1. Conceptual Model: Non-adherence, Poor Glucose Control, and Drug Therapy**

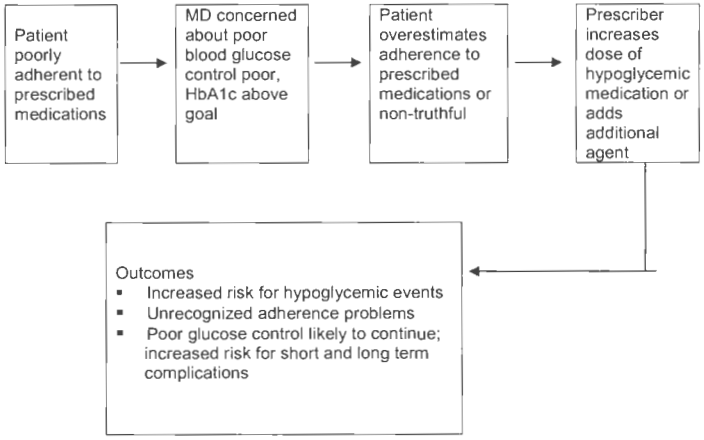
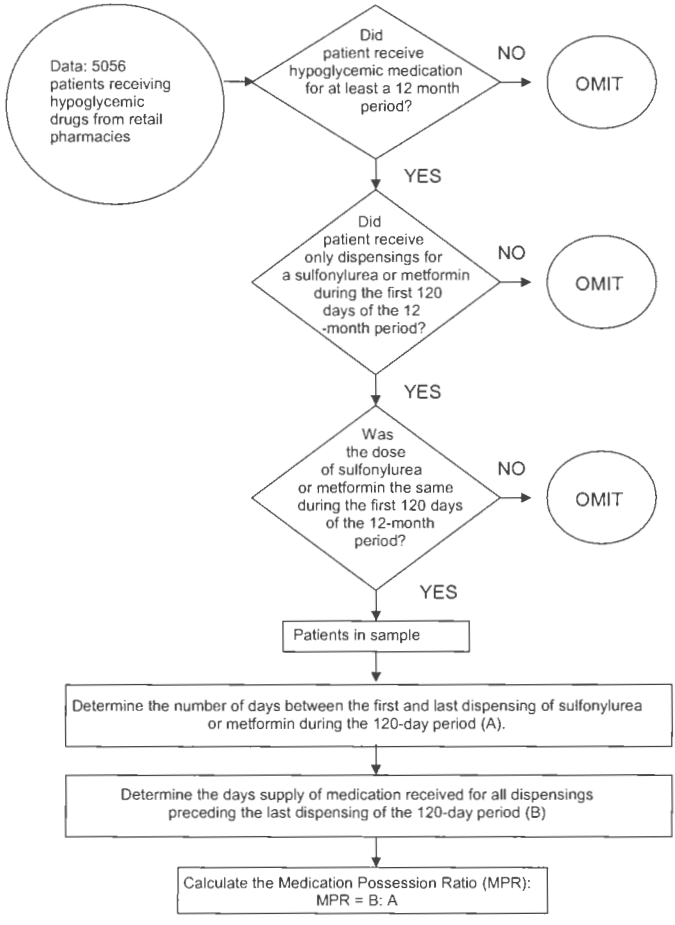


**Figure 2. Research Methodology: Identification of Users of Sulfonylurea or Metformin Mono-therapy and Determination of Non-adherence**




Research questions:
Is MPR < 8:10 associated with a dose change in the 8 months following first 120 days?
Is MPR < 8:10 associated with a medication change in the 8 months following first 120 days?
Is MPR < 8:10 associated with a dose change or a medication change in the 8 months following first 120 days?

**Table 1. Univariate Analyses: Patients Receiving Sulfonylurea or Metformin Mono-Therapy**

| | Sulfonylurea (N = 967) | | Metformin (N = 166) | |
|---|---|---|---|---|
| | n | % | n | % |
| Gender | | | | |
| Male | 572 | 59.2 | 85 | 51.2 |
| Female | 395 | 40.8 | 81 | 48.8 |
| Age | | | | |
| under 50 | 229 | 23.7 | 55 | 33.1 |
| 50-64 | 442 | 45.7 | 81 | 48.8 |
| 65 or older | 296 | 30.6 | 30 | 18.1 |
| Insurance | | | | |
| Plan A | 315 | 32.6 | 53 | 32.0 |
| Plan B | 527 | 54.5 | 95 | 57.2 |
| Other | 125 | 12.9 | 18 | 10.8 |
| Number of Rx Dispensed | | | | |
| under 5 | 151 | 15.6 | 31 | 18.7 |
| 5-15 | 550 | 56.9 | 95 | 57.2 |
| over 15 | 266 | 27.5 | 40 | 24.1 |

**Table 2. Medication Possession Among Patients Dispensed Only a Sulfonylurea or Only Metformin**

| | Sulfonylurea (N = 967) | | Metformin (N = 166) | |
|---|---|---|---|---|
| | n | % | n | % |
| Medication Possession Ratio (MPR) | | | | |
| ≥8:10 | 747 | 77.2 | 118 | 71.1 |
| ≥9:10 | 646 | 66.8 | 94 | 56.6 |
| Mean MPR | | 91.0 | | 86.6 |

**Table 3: Bivariate Analyses: Medication Possession Ratio (MPR) and Gender, Age Category, Insurance Type, and Number of Prescriptions Dispensed**

| | MPR < 8:10 Sulfonylurea users n = 967 % | MPR < 8:10 Metformin users n = 166 % |
|---|---|---|
| All subjects | 22.75 | 28.92 |
| Gender | | |
| Male | 22.72 | 29.41 |
| Female | 22.78 | 28.40 |
| Age | | |
| Under 50 | 33.19** | 36.36 |
| 50-64 | 19.46** | 27.16 |
| 65 or older | 19.59** | 20.00 |
| Insurance | | |
| Plan A | 24.80 | 33.33 |
| Plan B | 20.95 | 32.08 |
| Other | 23.34 | 26.32 |
| Number of Rx dispensed | | |
| < 5 | 41.72** | 45.16 |
| 5-15 | 22.00** | 26.32 |
| > 15 | 13.53** | 22.50 |

* $p < 0.05$, $X^2$
** $p < 0.01$, $X^2$

**Table 4a. Bivariate Analyses of Proportions: Sulfonylurea Sample**

| | Change of Dose % | Change of Drug % | Change of Drug or Dose % |
|---|---|---|---|
| All subjects (N = 967) | 58.53 | 26.78 | 62.67 |
| Gender | | | |
| Male | 59.01 | 25.70 | 62.59 |
| Female | 59.35 | 28.35 | 62.78 |
| Age | | | |
| Under 50 | 65.94** | 29.26** | 69.43* |
| 50-64 | 58.82 | 31.67** | 62.90 |
| 65 or older | 52.36** | 17.57** | 57.09* |
| Insurance | | | |
| Plan A | 62.40 | 24.00 | 68.00 |
| Plan B | 55.87 | 24.13 | 59.05 |
| Other | 59.20 | 29.03 | 63.57 |
| Number of Rx dispensed | | | |
| < 5 | 64.24 | 29.80 | 69.54 |
| 5-15 | 56.36 | 25.27 | 60.18 |
| > 15 | 59.77 | 28.20 | 63.91 |
| Medication Possession Ratio | | | |
| < 8:10 | 25.62* | 23.55 | 70.45** |
| < 9:10 | 18.70* | 22.46 | 60.37** |

* $p < 0.05$
** $p < 0.01$

**Table 4b. Bivariate Analyses of Proportions: Metformin**

| n = 166 | Change of Dose % | Change of Drug % | Change of Drug or Dose % |
|---|---|---|---|
| All subjects (N = 166) | 48.19 | 18.07 | 51.81 |
| Gender | | | |
| Male | 53.75 | 22.35 | 55.29 |
| Female | 48.84 | 13.58 | 48.15 |
| Age | | | |
| Under 50 | 54.55 | 23.64 | 58.18 |
| 50-64 | 46.91 | 13.58 | 49.38 |
| 65 or older | 40.00 | 20.00 | 46.67 |
| Insurance | | | |
| Plan A | 38.89 | 11.11 | 38.89 |
| Plan B | 50.94 | 18.87 | 56.60 |
| Other | 48.42 | 18.95 | 51.58 |
| Number of Rx dispensed | | | |
| < 5 | 58.06 | 16.13 | 61.29 |
| 5-15 | 45.26 | 17.89 | 47.37 |
| > 15 | 47.50 | 20.00 | 55.00 |
| Medication Possession Ratio | | | |
| < 8:10 | 32.50 | 30.00 | 56.25 |
| < 9:10 | 25.58 | 28.68 | 50.00 |

No significant differences among proportions

**Table 5a. Bivariate Logistic Regression Analysis, Sulfonylurea Sample: Dose Change**

| | ß | OR | CI low | CI high | Pr > $X^2$ |
|---|---|---|---|---|---|
| MPR < 8:10 | .404 | 1.497 | 1.094 | 2.049 | .0118 |
| Age | | | | | |
| Under 50* | | 1.0 | | | |
| 50-65 | -.304 | .738 | .529 | 1.029 | .0733 |
| 65 + | -.566 | .568 | .398 | .811 | .0018 |
| Male gender | -.141 | .986 | .760 | 1.293 | .9154 |
| Number of dispensings | | | | | |
| < 5 | | 1.0 | | | |
| 5-15 | -.330 | .719 | .495 | 1.044 | .8310 |
| > 15 | -.190 | .827 | .547 | 1.251 | .3684 |
| Insurance | | | | | |
| Plan A | | 1.0 | | | |
| Plan B | .137 | 1.146 | .864 | 1.520 | .3436 |
| Other insurance | .271 | 1.314 | .857 | 2.004 | .2119 |

**Table 5b. Bivariate Analyses of Metformin Sample: Change in Dose**

| | ß | OR | CI low | CI high | Pr > $X^2$ |
|---|---|---|---|---|---|
| MPR < .80 | .337 | 1.401 | .714 | 2.747 | .3268 |
| Age | | | | | |
| Under 50* | | | | | |
| 50-65 | -.306 | .736 | .370 | 1.464 | .3828 |
| 65 + | -.588 | .556 | .225 | 1.370 | .2020 |
| Male gender | .197 | 1.218 | .662 | 2.240 | .5271 |
| Number of Dispensings | | | | | |
| < 5 | | 1.0 | | | |
| 5-15 | -.516 | .597 | .263 | 1.356 | .2178 |
| > 15 | -.426 | .653 | .254 | 1.682 | .3778 |
| Insurance | | | | | |
| Plan A | | 1.0 | | | |
| Plan B | -.101 | .904 | .462 | 1.771 | .7686 |
| Other insurance | -.490 | .613 | .206 | 1.823 | .3785 |

**Table 6a. Bivariate Analyses of Sulfonylurea Sample: Change in Drug Dispensed**

| | ß | OR | CI low | CI high | Pr > $X^2$ |
|---|---|---|---|---|---|
| MPR < 8:10 | 0.062 | 1.064 | .759 | 1.490 | .7192 |
| Age | | | | | |
| Under 50* | | 1.0 | | | |
| 50-65 | .114 | 1.121 | .791 | 1.588 | .5206 |
| 65 + | -.663 | .515 | .341 | .779 | .0017 |
| Male gender | -.135 | .874 | .655 | 1.166 | .3596 |
| Number of dispensings | | | | | |
| < 5 | | | | | |
| 5-15 | -.227 | .797 | .535 | 1.186 | .2632 |
| > 15 | -.078 | .925 | .596 | 1.435 | .7278 |
| Insurance | | | | | |
| Plan A | | 1.0 | | | |
| Plan B | .252 | 1.286 | .935 | 1.771 | .1221 |
| Other insurance | -.007 | .993 | .612 | 1.613 | .9776 |

**Table 6b. Bivariate Analyses of Metformin Sample: Change in Drug Dispensed**

| | ß | OR | CI low | CI high | Pr > $X^2$ |
|---|---|---|---|---|---|
| MPR < 8:10 | .064 | 1.066 | .449 | 2.531 | .8849 |
| Age | | | | | |
| Under 50* | | 1.0 | | | |
| 50-65 | -.678 | .508 | .209 | 1.236 | .1352 |
| 65 + | -.214 | .808 | .272 | 2.401 | .7009 |
| Male gender | .605 | 1.832 | .811 | 4.139 | .1455 |
| Number of dispensings | | | | | |
| < 5 | | 1.0 | | | |
| 5-15 | .125 | 1.133 | .380 | 3.376 | .8222 |
| > 15 | .262 | 1.300 | .379 | 4.454 | .6762 |
| Insurance | | | | | |
| Plan A | | 1.0 | | | |
| Plan B | .005 | 1.005 | .426 | 2.372 | .9906 |
| Other insurance | -.622 | 0.538 | .106 | 2.724 | .4534 |

**Table 7: Chunk Test for Interactions**

| | DV | | -2log statistic | -2log difference | $X^2_{df=7}$: 14.07 |
|---|---|---|---|---|---|
| SFU | Dose Change | EV + V's* | 1288.97 | | |
| | | V's* | 1293.35 | 4.38 | NS |
| | Drug Change | EV + V's* | 1094.38 | | |
| | | V's* | 1099.10 | 4.73 | NS |
| | Dose or Drug Change | EV + V's* | 1252.29 | | |
| | | V's* | 1256.71 | 4.42 | NS |
| MET | Dose Change | EV + V's* | 213.28 | | |
| | | V's* | 223.98 | 10.70 | NS |
| | Drug Change | EV + V's* | 145.23 | | |
| | | V's* | 150.50 | 5.27 | NS |
| | Dose or Drug Change | EV + V's* | 213.54 | | |
| | | V's* | 221.79 | 8.24 | NS |
| SFU or MET | Dose Change | EV + V's* | 1520.58 | | |
| | | V's* | 1529.19 | 8.62 | NS |
| | Drug Change | EV + V's* | 1260.95 | | |
| | | V's* | 1267.154 | 6.20 | NS |
| | Dose or Drug Change | EV + V's* | 1487.08 | | |
| | | V's only* | 1494.36 | 7.28 | NS |

SFU = sulfonylurea sample
MET = metformin sample
* EV = Interaction terms; V = Lower order terms (independent variables)

**Table 8a. Multivariate Logistic Models of Sulfonylurea Sample: Change in Dose**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3485 | 1.4169 | 0.1655 | 1.0244 | 1.9599 | 0.0353 |
| Age | | | | | | |
| under50 | - | 1.0 | | | | |
| 50-64 | -0.2529 | 0.7765 | 0.1735 | 0.5527 | 1.0911 | 0.1449 |
| 65+ | -0.5283 | 0.5896 | 0.1855 | 0.4099 | 0.8481 | 0.0044 |
| Male Gender | -0.0039 | 0.9961 | 0.1356 | 0.7636 | 1.2994 | 0.977 |
| Insurance | | | | | | |
| Plan A | - | 1.0 | | | | |
| Plan B | 0.1121 | 1.1186 | 0.1457 | 0.8407 | 1.4884 | 0.4416 |
| Other | 0.2584 | 1.2949 | 0.2196 | 0.8420 | 1.9914 | 0.2393 |
| Total Dispensings | | | | | | |
| 0-4 | - | 1.0 | | | | |
| 5-15 | -0.2086 | 0.8117 | 0.1960 | 0.5528 | 1.1919 | 0.2871 |
| 16+ | 0.0055 | 1.0056 | 0.2214 | 0.6516 | 1.5519 | 0.9801 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3569 | 1.4289 | 0.1622 | 1.0398 | 1.9637 | 0.0277 |
| Age | | | | | | |
| under50 | - | 1.0 | | | | |
| 50-64 | -0.2575 | 0.7730 | 0.1713 | 0.5525 | 1.0814 | 0.1328 |
| 65+ | -0.5212 | 0.5938 | 0.1831 | 0.4148 | 0.8502 | 0.0044 |

**Table 8b. Multivariate Logistic Models of Sulfonylurea Sample: Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.0236 | 1.0239 | 0.1793 | 0.7205 | 1.4550 | 0.8953 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | 0.1256 | 1.1338 | 0.1821 | 0.7935 | 1.6201 | 0.4904 |
| 65+ | -0.6453 | 0.5245 | 0.2148 | 0.3443 | 0.7991 | 0.0027 |
| Male Gender | -0.1077 | 0.8979 | 0.1507 | 0.6683 | 1.2064 | 0.4748 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | 0.2372 | 1.2677 | 0.1653 | 0.9169 | 1.7528 | 0.1513 |
| Other | 0.0161 | 1.0162 | 0.251 | 0.6214 | 1.6621 | 0.9489 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.2264 | 0.7974 | 0.2101 | 0.5282 | 1.2037 | 0.2811 |
| 16+ | -0.0562 | 0.9454 | 0.2377 | 0.5933 | 1.5064 | 0.8131 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | 0.1141 | 1.1209 | 0.1776 | 0.7914 | 1.5876 | 0.5206 |
| 65+ | -0.6631 | 0.5153 | 0.2108 | 0.3409 | 0.7789 | 0.0017 |

**Table 8c. Multivariate Logistic Models of Sulfonylurea Sample: Change in Dose or Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3861 | 1.4712 | 0.171 | 1.0523 | 2.0570 | 0.0239 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2256 | 0.7980 | 0.1781 | 0.5629 | 1.1314 | 0.2052 |
| 65+ | -0.4852 | 0.6156 | 0.1896 | 0.4245 | 0.8926 | 0.0105 |
| Male Gender | 0.0036 | 1.0035 | 0.1382 | 0.7654 | 1.3158 | 0.9796 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | 0.1694 | 1.1846 | 0.1478 | 0.8867 | 1.5826 | 0.2516 |
| Other | 0.3732 | 1.4524 | 0.2263 | 0.9321 | 2.2631 | 0.0991 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.2851 | 0.7520 | 0.2028 | 0.5054 | 1.1191 | 0.1598 |
| 16+ | -0.0520 | 0.9493 | 0.2286 | 0.6065 | 1.4860 | 0.8199 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR | 0.4046 | 1.4987 | 0.1674 | 1.0795 | 2.0807 | 0.0157 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2406 | 0.7862 | 0.1757 | 0.5571 | 1.1093 | 0.171 |
| 65+ | -0.4846 | 0.6159 | 0.187 | 0.4269 | 0.8886 | 0.0095 |

**Table 9a. Multivariate Logistic Models of Metformin Sample: Change in Dose**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.2252 | 1.2526 | 0.3564 | 0.6229 | 2.5187 | 0.5274 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.3241 | 0.7232 | 0.3604 | 0.3568 | 1.4656 | 0.3685 |
| 65+ | -0.6631 | 0.5153 | 0.4976 | 0.1943 | 1.3664 | 0.1827 |
| Male Gender | 0.1763 | 1.1928 | 0.3232 | 0.6331 | 2.2474 | 0.5853 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | -0.0468 | 0.9543 | 0.3593 | 0.4719 | 1.9298 | 0.8964 |
| Other | -0.738 | 0.4781 | 0.5839 | 0.1522 | 1.5015 | 0.2063 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.6359 | 0.5295 | 0.4617 | 0.2142 | 1.3087 | 0.1684 |
| 16+ | -0.3006 | 0.7404 | 0.513 | 0.2709 | 2.0236 | 0.5578 |

*No significant terms*

**Table 9b. Multivariate Logistic Models of Metformin Sample: Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.0461 | 1.0471 | 0.4619 | 0.4234 | 2.5891 | 0.9206 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.7268 | 0.4835 | 0.4639 | 0.1947 | 1.2001 | 0.1172 |
| 65+ | -0.2083 | 0.8120 | 0.6069 | 0.2471 | 2.6677 | 0.7314 |
| Male Gender | 0.6746 | 1.9632 | 0.4251 | 0.8533 | 4.5168 | 0.1125 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | 0.2825 | 1.3264 | 0.5784 | 0.4269 | 4.1213 | 0.6252 |
| 16+ | 0.4662 | 1.5939 | 0.665 | 0.4329 | 5.8685 | 0.4833 |

*No significant terms*

**Table 9c. Multivariate Logistic Models of Metformin Sample: Change in Dose or Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.1441 | 1.155 | 0.3608 | 0.5695 | 2.3426 | 0.6895 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.4277 | 0.652007 | 0.3659 | 0.3183 | 1.3357 | 0.2425 |
| 65+ | -0.6356 | 0.529618 | 0.4999 | 0.1988 | 1.4109 | 0.2036 |
| Male Gender | 0.3149 | 1.370122 | 0.3258 | 0.7235 | 2.5947 | 0.3336 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | -0.1544 | 0.856929 | 0.3634 | 0.4204 | 1.7469 | 0.6709 |
| Other | -1.0509 | 0.349623 | 0.5875 | 0.1105 | 1.1058 | 0.0737 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.0706 | 0.931835 | 0.4704 | 0.3706 | 2.3429 | 0.1326 |
| 16+ | -0.1438 | 0.866061 | 0.5227 | 0.3109 | 2.4126 | 0.7832 |

*No significant terms*

**Table 10a. Multivariate Logistic Models of Population of Combined Sulfonylurea and Metformin Samples: Change in Dose**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3102 | 1.3637 | 0.1489 | 1.0185 | 1.8258 | 0.0372 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2368 | 0.7891 | 0.1549 | 0.5825 | 1.0691 | 0.1264 |
| 65+ | -0.4821 | 0.6175 | 0.1697 | 0.4428 | 0.8611 | 0.0045 |
| Male Gender | 0.0356 | 1.0362 | 0.1236 | 0.8133 | 1.3203 | 0.7736 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | 0.0838 | 1.0874 | 0.134 | 0.8362 | 1.4140 | 0.5319 |
| Other | 0.1523 | 1.1645 | 0.2024 | 0.7832 | 1.7315 | 0.4517 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.2505 | 0.7784 | 0.1779 | 0.5493 | 1.1032 | 0.1591 |
| 16+ | -0.0311 | 0.9694 | 0.2017 | 0.6528 | 1.4394 | 0.8776 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3239 | 1.3825 | 0.146 | 1.0385 | 1.8405 | 0.0265 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2421 | 0.7850 | 0.1531 | 0.5815 | 1.0597 | 0.1139 |
| 65+ | -0.4717 | 0.6239 | 0.1672 | 0.4496 | 0.8659 | 0.0048 |

**Table 10b. Multivariate Logistic Models of Population of Combined Sulfonylurea and Metformin Samples: Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.0077 | 1.0077 | 0.1654 | 0.7287 | 1.3936 | 0.9628 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | 0.0351 | 1.0356 | 0.1672 | 0.7462 | 1.4372 | 0.8341 |
| 65+ | -0.5959 | 0.5511 | 0.2001 | 0.3723 | 0.8157 | 0.0029 |
| Male Gender | -0.0111 | 0.9890 | 0.1406 | 0.7508 | 1.3027 | 0.9373 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | 0.2098 | 1.2334 | 0.154 | 0.9121 | 1.6680 | 0.1732 |
| Other | -0.0385 | 0.9622 | 0.238 | 0.6035 | 1.5342 | 0.8714 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.1818 | 0.8338 | 0.1958 | 0.5680 | 1.2238 | 0.3531 |
| 16+ | 0.0279 | 1.0283 | 0.2216 | 0.6660 | 1.5876 | 0.9001 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | 0.0345 | 1.0351 | 0.1634 | 0.7514 | 1.4258 | 0.8329 |
| 65+ | -0.5945 | 0.5518 | 0.1959 | 0.3759 | 0.8101 | 0.0024 |

**Table 10c. Multivariate Logistic Models of Population of Combined Sulfonylurea and Metformin Samples: Change in Dose or Change in Drug Dispensed**

All Independent Variables

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3255 | 1.3847 | 0.1526 | 1.0268 | 1.8675 | 0.0329 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2277 | 0.7964 | 0.1583 | 0.5839 | 1.0861 | 0.1504 |
| 65+ | -0.4374 | 0.6457 | 0.1727 | 0.4603 | 0.9058 | 0.0113 |
| Male Gender | 0.0575 | 1.0592 | 0.1255 | 0.8282 | 1.3546 | 0.6468 |
| Insurance | | | | | | |
| Plan A | | 1.0 | | | | |
| Plan B | 0.1185 | 1.1258 | 0.1357 | 0.8629 | 1.4688 | 0.3829 |
| Other | 0.2116 | 1.2357 | 0.2067 | 0.8240 | 1.8529 | 0.3058 |
| Dispensings | | | | | | |
| 0-4 | | 1.0 | | | | |
| 5-15 | -0.3211 | 0.7254 | 0.183 | 0.5068 | 1.0384 | 0.0793 |
| 16+ | -0.0563 | 0.9453 | 0.2072 | 0.6298 | 1.4188 | 0.7858 |

Final Model

| | Beta | OR | se | CI low | CI High | Pr > X2 |
|---|---|---|---|---|---|---|
| MPR < 8:10 | 0.3444 | 1.4111 | 0.1496 | 1.0525 | 1.8920 | 0.0213 |
| Age | | | | | | |
| under50 | | 1.0 | | | | |
| 50-64 | -0.2377 | 0.7884 | 0.1564 | 0.5803 | 1.0713 | 0.1285 |
| 65+ | -0.4275 | 0.6521 | 0.1701 | 0.4672 | 0.9102 | 0.0120 |

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**Adherence to Hypoglycemic Therapy Among Patients Prescribed Monotherapy with a Sulfonylurea or Metformin, and Dual Therapy With Both Agents**


## ABSTRACT

**Background** Adherence to prescribed drug therapies for chronic conditions is known to be poor. Lack of optimal adherence to drug therapies for diabetes is particularly problematic, since poor glucose control has been associated with an increased risk of certain types of diabetic complications.

**Objective** To determine if diabetic patients prescribed dual therapy with both a sulfonylurea and metformin as separate prescriptions are more likely to be nonadherent than patients receiving monotherapy with either agent.

**Methods** A cross-sectional study examining retail pharmacy dispensings to diabetic patients receiving oral hypoglycemic therapy. Patients receiving monotherapy with either a sulfonylurea or metformin and patients receiving dual therapy with both drugs were identified. The medication possession ratio (MPR) was used to assess adherence, as the days supply of all hypoglycemic medication dispensed to the number of days between first and last dispensings. The influence of the type of therapy prescribed (dual or

monotherapy) on medication possession was assessed. Other factors investigated as potential influences of medication possession included age, gender, insurance plan associated with the dispensing, the total number of dispensings, and dispensings for selected anti-depressant medications. Multivariate logistic regression was used estimate the likelihood of nonadherence among those receiving dual therapy, and controlling for potential confounding variables.

**Results** Overall, 71% of patients possessed medication for at least 80% of days during the assessment period, and 59% of patients possessed medication for at least 90% of days. Patients who received only dispensings for a sulfonylurea were most frequently in possession of medication (MPR ≥ 8:10: 77%, MPR ≥9:10: 67%). Patients who received dispensings only for metformin were less frequently in possession of medication for at least 80% and 90% of days (MPR ≥8:10: 71%, MPR ≥9:10: 67%). Medication possession was lowest among patients receiving dispensings for both a sulfonylurea and metformin, with 57% of such patients possessing medication for at least 80% of days, and 43% of such patients possessing medication for at least 90% of days. Using multivariate logistic models controlling for the effects of age and the number of dispensings, we determined that patients receiving dual therapy with a sulfonylurea and metformin were more than 3 times more likely to fail to possess medication for at least 80% of days (OR 3.14, 95% CI 2.42 – 4.08) or 90% of days (OR 3.20, 95% CI 2.49 – 4.11).

**Conclusions** As determined using the medication possession ratio, adherence to oral hypoglycemic drug therapies was frequently sub-optimal. Patients that possessed medication for less than 80% of days were likely not achieving tight control of blood glucose. Adherence was poorest among those receiving the combination of a sulfonylurea plus metformin.

The success of intensive therapy in tightly controlling the blood glucose level is contingent upon patient behavior. Though perhaps difficult to predict, adherence can be assessed. Diabetes management strategies should include the assessment of adherence with prescribed hypoglycemic drug regimens, and the application of interventions designed to improve adherence. Additionally, the complexity of the drug regimen should be considered as a potential barrier to optimal adherence.

## INTRODUCTION

Non-adherence to prescribed drug regimens is a primary cause of sub-optimal health outcomes. Despite the efforts of prescribers and pharmacists, as many as one-half of patients or more will not achieve the full benefit of prescribed medications due to problems with adhering to therapy (1, 2). Various types of interventions intended to improve adherence rates have been studied. However, research has not uncovered any specific intervention that effectively improves adherence to the degree where the full benefit of therapy is realized (3-5). The utility of such interventions ultimately depends upon the ability of health care providers to identify non-adherence with treatment regimens and, most importantly, depends upon characteristics of individual patients (6).

Further complicating the picture, despite greater than two decades of study regarding adherence with prescribed therapies, researchers have been mostly unable to consistently demonstrate associations between the behavior of adherence and various potential predictive factors (7). For example, some researchers have reported an association between adherence with prescribed therapies and age (8, 9), gender (9, 10), and race (11, 12), though others have not (13, 14). Beyond such patient-specific factors, researchers have attempted to understand and describe the underlying psychological determinants of adherence. Models borrowed from the psychological sciences have been used to characterize and predict the behavior of adherence with

some success. For example, the health belief (15), self-efficacy (16), and stages-of-change models (17) have all been shown to be useful in explaining adherence to drug therapy.

Factors specific to the drug regimen prescribed have also been examined as potential influences of adherence to therapy. Regimens having increased complexity and greater behavioral demand have been shown to be associated with decreased adherence (18, 19). The number of drugs prescribed and number of required daily dosages have been shown to be associated with adherence, with the probability of non-adherence increasing in patients prescribed multiple medications and receiving divided daily doses (20, 21). This phenomenon has been perhaps best demonstrated in studies of patients treated for hypertension (22-24) and human immunodeficiency virus infection (25). The cost of and access to medications may also be important barriers to adherence for some patients.

Adherence to drug therapies prescribed for diabetes is particularly important. Hypoglycemic therapy is essential for preventing acute complications resulting from elevated blood glucose, such as the nonketotic hyperosmolar state. Additionally, tight control of blood glucose has been demonstrated to reduce the incidence of several types of chronic diabetic complications (26-28). For the majority of diabetic patients, such tight control of blood sugar can only be achieved through rigid adherence to the prescribed hypoglycemic drug

regimen. Poor adherence to prescribed drug regimens would expectedly result in sub-optimal blood glucose control, as demonstrated by Kavanagh et al (29). In the longer term, patients that do not adhere to hypoglycemic drug regimens are at increased risk for developing complications such as blindness, neuropathy, and kidney disease.

In this study, we sought to determine if the complexity of the drug regimen was an influence of adherence to therapy. Specifically, we hypothesized that diabetic patients would be less likely to adhere to regimens that utilized two drugs as compared with regimens consisting of a single hypoglycemic agent. To test this hypothesis, we used pharmacy data to assess hypoglycemic drug utilization among patients receiving dispensings for a sulfonylurea, metformin, or both of these agents together but as separate tablets.

## METHODS

### Population

We conducted a cross-sectional study using data provided by Consumer Value Stores, Inc (CVS). The data included over one-quarter million dispensings to 5056 diabetic patients between April 1997 and May 1999. Most patients included in this population were enrollees of one of two area health plans, and were participants in a special managed care program in diabetes. Patients were restricted to designated CVS pharmacies for their pharmacy services, and all dispensings from these pharmacies were included in the data provided for research. The restriction of patients to these designated pharmacies was deemed an advantageous feature, potentially resulting in a more complete representation of pharmacy utilization and thus reducing the likelihood of misclassification of non-adherence.

From the population of all patients included in the sample provided, we identified those that received a dispensing for any hypoglycemic medication during a 12-month period. Patients that did not receive dispensings for any class of hypoglycemic medication were not included in the sample. The hypoglycemic medication dispensed did not need to be the same throughout all 12 months. From those identified as receiving at least one hypoglycemic drug during a 12-month period, we selected patients that received either a sulfonylurea or metformin, or both during the first four months of this 12-month

period. Patients who received a hypoglycemic drug other than a sulfonylurea or metformin during this four-month period were excluded from the sample. Thus, the final sample included only patients that received dispensings for a sulfonylurea and/or metformin during a four-month period, and received some type of hypoglycemic medication throughout a 12-month period. Patients were classified by type of hypoglycemic drug regimen prescribed: either mono-therapy with sulfonylurea or metformin, or dual therapy using both drugs.

**Calculating the medication possession ratio**

We used the medication possession ratio (MPR) as the measure of adherence with prescribed hypoglycemic drug therapy, defined as the number of days that a patient was in possession of medication. The use of the medication possession ratio for assessing adherence is described by Fairman and Motheral (30).

To calculate the MPR, we determined the total days supply of medication received for all dispensings preceding the last dispensing of the four-month period. A ratio was created using the days supply of medication received and the number of days between the first and last dispensing during this four-month period. For example, the MPR for a patient that received three dispensings of 30 tablets each (90 tablets) during a period of 113 days would be 90:113, or roughly 8:10. Patients who received only one dispensing during

the four-month period but who received medication in subsequent months were classified as non-adherent. There were 19 such patients (1.1%).

We assessed adherence using MPR thresholds of 8:10 and 9:10. Non-adherence was defined as failing to possess medication for at least 80% or 90% of days in the period. For example, the patient that received 90 tablets in 113 days would be classified as adherent using the 8:10 threshold, but classified as non-adherent using the 9:10 threshold. Results based upon these two MPR thresholds were presented separately. For patients dispensed both sulfonylurea and metformin as dual therapy, non-adherence was defined as failing to possess either medication for a number of days sufficient to cover eight of ten or nine of ten days in the period. Thus, patients prescribed both drugs must have adhered to both medications to be classified as adherent.

The MPR threshold of 8:10 has been used in previous studies. Some researchers have used a ratio of 8:10, or 80% of days covered, in studies of adherence to other chronic therapies such as hormone-replacement therapy (31); hypertension (24, 32); and depression (33). Additionally, we also used second MPR threshold of 9:10 to define adherence based on estimates of what might be required to achieve tight glycemic control.

**Potential confounding variables**

In addition to the type of hypoglycemic drug regimen prescribed, we assessed the influence of five other potential confounding factors that were derivable from the pharmacy data provided. Three of these variables, age, gender, and insurance type, were obtainable from the patient profile. We stratified age into three categories: < 50, 50-64, and 65 years of age or older; representing younger, middle-aged, and senior patients. Insurance type was also categorized into three types. Of all insurances associated with prescription refills, two area health plans accounted for nearly 90% of all dispensings. These two insurance types were classified as health plan A and health plan B. A third category of insurance type included patients whose prescription coverage was an insurance type other than health plan A or B, or patients that paid cash for all dispensings. In cases where more than one insurance type (or cash) was identified, the insurance type associated with the first non-cash dispensing was used.

We also sought to examine the effect of the number of medications prescribed, hypothesizing that a greater number of prescriptions would be associated with a greater likelihood of non-adherence to therapy. For this variable, we determined the total number of dispensings during the four-month period, including medications for conditions other than diabetes.

DiMatteo et al found depression to be a risk factor for non-adherence with prescribed drug therapies (34). Thus, we also decided to include a fifth potential confounding variable representing patients who had received an anti-depressant medication. We decided not to include patients receiving an tricyclic anti-depressant in our categorization method, since the popularity of these agents for use in depression is declining (35, 36) and these agents are used for conditions other than depression (37-41). Patients were considered to have depression if they received at least one dispensing for a medication presented in table1.

**Statistical methods**

Univariate statistics were used to determine the frequency and percentage of patients that received dispensings for a sulfonylurea, metformin, or both. The frequency and percentage of patients having a medication possession ratio percentage of at least 8:10 and 9:10 was determined, overall and for each type of regimen prescribed. The frequency and percentage of the potential confounding variables described above was also determined for each of the regimen types and overall.

For initial evaluation, the total number of dispensings was categorized into three groups: less than 5 dispensings, 5-15 dispensings, and greater than 15 dispensings. These three groupings reflected quartiles of the frequency

distribution for this variable, with the category of 5-15 dispensing representing a combination of the inner quartiles.

For inclusion in logistic models, categories of the continuous variables age and total number of prescriptions dispensed were based upon association with medication possession, the dependent variable. Parametric form was assessed by plotting quartiles of the frequency distribution for these continuous variables with MPR thresholds of 8:10 and 9:10. The resulting strata for age and the dichotomization of the total number of dispensings reflect the results of this assessment.

Chi-square analyses were used to assess bivariate relationships between proportions for all independent variables and the medication possession ratio. Bivariate logistic models were also constructed, with separate models assessed for each independent variable and the medication possession ratio. For the dependent variable of medication possession, ratio thresholds of 8:10 and 9:10 were assessed. Multivariate statistics were used to identify the presence of collinearity between independent variables, to determine the presence of interactions between variables, and to assess the association between type of regimen prescribed and medication possession, controlling for other potential confounding variables. Collinearity diagnostics were performed using the PROC REG procedure for multiple regression as suggested by Allison (42). Collinearity between independent variables was assessed

separately for MPR thresholds of 8:10 and 9:10. The presence of collinearity was determined using thresholds for condition index and proportion of shared variance as described by Tabachnick and Fidell (43).

The likelihood ratio test was used to test for interaction between variables in multivariate logistic models, using the chunk test as described by Kleinbaum (44). For this procedure, we calculated the difference in the –2log statistic between full and reduced models. Full models included all possible interaction and single terms; reduced models included single terms only. The difference in –2log statistic between full and reduced models was tested for significance using the chi-square distribution with alpha .05, and with degrees of freedom equal to the difference in terms between the two models. A difference in –2log value that was less than the chi-square statistic was considered sufficient evidence that the model could not be better fit by including interaction between variables.

Various multivariate models were assessed. Initial models contained all independent variables: non-significant terms were removed to create several other models. When non-significant terms were removed from models, we examined the magnitude of change in the parameter estimate beta and confidence interval for the variable regimen type (dual or monotherapy). The association between regimen type and medication possession is presented in

a summary table that presents the parameter estimate, standard error, odds ratio, and 95% confidence interval obtained for each model.

## RESULTS

A total of 1537 patients were identified as receiving dispensings for either a sulfonylurea, metformin, or both. Of these three types of hypoglycemic drug regimens, a majority of patients were classified as users of sulfonylurea only (n = 967; 63%). A total of 404 patients (26%) were determined to be users of both sulfonylurea and metformin. A lesser number of patients were classified as users of metformin only (n =166; 11%).

Table 2 presents the frequency and percentage of several characteristics the population, and within each regimen type. For all categories of drug therapy, patients were most frequently male and between the ages of 50-64. Approximately half of patients in each of the three regimen categories were between the ages of 50 and 64. More than half of patients in each among each regimen type were identified as having insurance plan B. Insurance types plan A and plan B accounted for 87-89% of all subjects.

Patients dispensed only sulfonylureas were least frequently dispensed a medication for an anti-depressant (11%), as compared to those receiving monotherapy with metformin (13%) or dual therapy with sulfonylurea plus metformin (16%). Of all patients studied, 13% received a dispensing for one of the antidepressant medications presented in figure 1.

The frequency and percent of patients possessing medication for at least 80% and 90% of days is presented in Table 3. Patients receiving dispensings for only a sulfonylurea were most frequently determined to have medication possession ratios greater then 8:10 and 9:10 (77% and 69% respectively). Patients receiving dispensings for only metformin were less frequently identified as having an MPR above 0.80 and 0.90 (71% and 57%). Patients dispensed both sulfonylurea and metformin were least frequently identified as having an MPR greater than 8:10 (57%) or 9:10 (43%). Overall, 71% of patients possessed enough medication for 8 of 10 days, and 60% of patients possessed a quantity of medication sufficient to be able to adhere to therapy at least 90% of days.

The relationship between medication possession and other potential confounding variables is presented in Tables 4a and 4b. For both users of only sulfonylureas and among the total sample, patients under 50 years of age were most frequently identified as having an MPR less than 8:10 or 9:10 ($p < 0.01$). Among those dispensed both a sulfonylurea and metformin, those under 50 years of age were also more frequently categorized as having MPR less than 8:10 or 9:10, though this result was statistically significant only for the MPR threshold of less than 8:10 ($p < 0.05$). Subjects 65 years of age or older were least frequently identified as having an MPR less than 8:10 or 9:10 ($p < 0.01$). The percentage of males and females having an MPR < 0.80 or 0.90 did not differ significantly for any of the regimen types or overall.

Likewise, type of insurance did not differ significantly between groups for either MPR threshold.

Patients receiving greater than 15 total dispensings were least frequently categorized as having an MPR less than 8:10 or 9:10, and those dispensed less than 5 prescriptions were most frequently categorized as not possessing a sufficient quantity of medication using either MPR threshold. These differences were statistically significant overall, and among the group of patients receiving dispensings for sulfonylurea only ($p < 0.01$ for each). The lesser number of patients in the metformin only and in the metformin plus sulfonylurea regimen categories likely affected the ability to detect a statically significant difference for these groups.

Among patients dispensed sulfonylureas, those who received a dispensing for a medication for depression more frequently had an MPR less than 8:10 or 9:10 ($p < 0.05$). The percentage of patients who were prescribed an anti-depressant did not differ in statistical significance for other regimen categories or overall.

To determine the appropriate form for inclusion into logistic models, the parametric form of the continuous variables age and number of dispensings was assessed. Age was relatively linearly related to the MPR, with the likelihood of being categorized as having an MPR less than 8:10 or 9:10

decreasing with advancing age. Age categories used for analyses were based upon the frequency distribution of ages and for ease in presentation and interpretation. We did not find the presence of a strong linear trend between the total number of dispensings and the MPR. However, patients receiving 12 or more dispensings were less likely to be classified as having an MPR less than 8:10 or 9:10, while a total of less than 12 dispensings did not prove to be associated with the MPR. Thus, for use in logistic models, we dichotomized the total number of dispensings at 12 prescriptions.

Tables 5a and 5b present the results of bivariate logistic models for each independent variable using MPR thresholds of 8:10 and 9:10. As compared with patients receiving dispensings for either a sulfonylurea or metformin only, those receiving dispensings for both drugs were more likely to be classified as having and MPR less than 8:10 (OR 2.4; 95% CI 1.9 – 3.1) or less than 9:10 (OR 2.49; 95% CI 1.97 – 3.14). Age was also significantly associated with medication possession. As compared with patients less than 50 years of age, patients who were 50-65 years of age and 65 years or older were less likely to be classified with an MPR less than 8:10 (age 50-65 OR 0.55: 95% CI 0.42 – 0.71; age 65 or older OR 0.48: 95% CI 0.35 – 0.65), and less likely to be classified as having an MPR less than 9:10 (age 50-65 OR 0.60: 95% CI 0.46 – 0.76; age 65 or older OR 0.58: 95% CI 0.44 – 0.76). The total number of dispensings was also associated with medication possession, as those

receiving 12 or more dispensings were less likely to have an MPR less than 8:10 (OR 0.56: 95% CI 0.45 – 0.71) or 9:10 (OR 0.57: 95% CI 0.47 – 0.70).

Receiving a dispensing for an anti-depressant medication increased the likelihood of being classified as having an MPR less than 8:10 or 9:10, though the association was not statistically significant (MPR < 8:10 OR 1.27: 95% CI 0.92 – 1.75; MPR < 9:10 OR 1.21: 95% CI 0.89 – 1.64). Gender and type of insurance did not appear to influence the likelihood of being classified as having an MPR less than 8:10 or 9:10 in bivariate logistic models.

Multivariate logistic analyses were performed to control for potential confounding factors while assessing the association between type of regimen (one drug or two) and medication possession. The results of a multivariate model including all independent variables are presented in Table 7a (MPR less than 8:10) and Table 7b (MPR less than 9:10). Compared to those receiving dispensings for only a sulfonylurea or metformin, patients receiving dispensings for both a sulfonylurea and metformin (dual therapy) were more than three times as likely to be classified as having an MPR less than 8:10 (MPR < 8:10: OR 3.12, 95% CI 2.40 – 4.06; MPR < 9:10 OR 3.20, 95% CI 2.49 – 4.12). In these models, age and more than 12 total dispensings were also shown to be associated with medication possession. Receiving a dispensing for an anti-depressant was a non-significant contributor to this model (MPR < 8:10: OR 1.36, 95% CI 0.96 – 1.92; MPR < 9:10: OR 1.31, 95%

CI 0.94 – 1.82). Gender and insurance type were not found to be associated with medication possession using either the 8:10 or 9:10 thresholds.

Tables 8a and 8b present the results of multivariate models containing only the significant terms: regimen type, age category and total number of dispensings. Removing the non-significant variables (gender, insurance type, and received anti-depressant medication) resulted in little change in the likelihood of being categorized as having an MPR less than 8:10 or 9:10 among those prescribed dual therapy. It this model, patients who received dispensings for both a sulfonylurea and metformin remained more than 3 times more likely to be classified as having an MPR less than 8:10 or 9:10. (MPR < 8:10: OR 3.14, 95% CI 2.42 – 4.08; MPR < 9:10: OR 3.20, 95% CI 2.49 – 4.11). To assess the influence of the total number of dispensings, we included only the terms for regimen type and age category in another logistic model (Tables 9a and 9b). Without controlling for the number of prescriptions dispensed, patients receiving dispensings for both a sulfonylurea and metformin remained less likely to possess medication, though the effect was lessened as compared to models that included this factor (MPR < 8:10: OR 2.47, 95% CI 1.93 – 3.14; MPR < 9:10 OR 2.51, 95% CI 1.99 – 3.18). In the models including only regimen type and age category, the effect of regimen type on medication possession was similar to what was found for the bivariate analyses presented in tables 5a and 5b. Parameter estimates (beta) for the

regimen type and associated standard errors and 95% confidence intervals for each of the models described above are presented in tables 10a and 10b.

## DISCUSSION

Medication possession was highest among patients that were dispensed only sulfonylureas, with 77% and 67% of such patients possessing medication for at least 80% and 90% of days, respectively. Medication possession was next highest among patients dispensed only metformin, with 71% of such patients possessing medication for at least 8 of 10 days, and 57% of patients possessing mediation for 9 of 10 days. Patients that received dispensings for both drugs were less frequently in possession of medication. Only 57% of such patients possessed enough medication to be adherence 80% of days, and less than half of patients prescribed both drugs (43%) possessed enough medication to cover 90% of days in the period. Overall, 71% of all patients possessed medication for at least 8 of 10 days, and only 60% of patients possessed medication for 9 of 10 days. In all models, dual therapy with a sulfonylurea plus metformin was associated with an increased likelihood of non-adherence as defined as medication possession, as compared with monotherapy with either a sulfonylurea or metformin.

These results provide evidence that the self-management of diabetes is far from ideal for many patients. Clearly, patients who are not in possession of medication cannot be achieving the 'tight control' of blood glucose that has been demonstrated to reduce the incidence of many types of diabetes complications. Unfortunately, the finding that many diabetic patients do not strictly adhere to prescribed hypoglycemic drug regimens is not unexpected.

Other researchers have provided evidence that adherence to hypoglycemic therapy is often sub-optimal. Venturini et al (45) reported a mean medication possession percentage of 83% of days among HMO patients prescribed a sulfonylurea. In a study using Medicaid claims data, Sclar et al (46) found that only 39.4% of newly treated diabetics receiving a second-generation sulfonylurea obtained at least 6 months supply of medication during a 12-month period. In an assessment of hypoglycemic drug possession among nearly 3,000 Scottish diabetics, Morris et al (47) found that roughly one-third of patients prescribed sulfonylureas received enough medication to cover 90% of days. Poor adherence to prescribed therapies among diabetic patients has been described by several researchers (48-53).

The primary aim of this study was to determine if adherence to prescribed drug regimens was poorer among patients prescribed dual therapy with a sulfonylurea plus metformin as compared with patients receiving only one medication as monotherapy. Indeed, patients prescribed the two hypoglycemic drugs together were less likely to possess medication. In addition, the difference in adherence was pronounced. As compared with patients receiving dispensings for only a sulfonylurea or metformin, the percentage of patients having a medication possession ratio less than 8:10 or 9:10 was significantly greater for patients receiving both drugs. Logistic models provided an estimate of influence, with the odds of non-adherence as measured in terms of medication possession ranging from 2.4 to 3.1 times

greater for those prescribed both medications as compared with patients receiving monotherapy, depending upon inclusion of other factors in the model.

Morris et al (47) reported similar findings when comparing medication possession rates among Scottish diabetics who received dispensings for either sulfonylurea, metformin, or both. During a period of up to three-years, only 31% of patients using a sulfonylurea, and 34% of patients using metformin possessed enough medication to achieve adequate adherence, defined as possessing medication for 90% of days during the period.

An influence of the number of medications prescribed on adherence has also been described. Sellors and Hayes (54) note that in general the probability of non-adherence can be expected to increase with the number of medications prescribed. Treatment complexity has been shown to be a barrier to adherence in diabetic patients (55). In other health conditions, the number of medications prescribed has been shown to be an influence of drug utilization. For example, persistence with a single-pill combination of two anti-hypertensive agents was found to be superior to persistence rates when the same agents were prescribed as separate pills (56). Additionally, treatment complexity is a recognized feature of adherence to drug therapies for human immunodeficiency virus (57, 58).

The age of the patient was also found to be associated with medication possession. In this study, bivariate analyses revealed that patients 50 years of age or older were less likely to be categorized as non-adherent. This finding is consistent with research by Sclar, who also found older diabetic patients to be more likely to obtain oral hypoglycemic medication regularly (46). This finding is explainable using the health beliefs model as described by Becker (59). According to this model, patients that perceive their disease to pose a threat to health will be more likely to adhere to therapies that they perceive will lessen the risk of illness. Thus, in this study, perhaps younger diabetic patients were poorly adherent to drug therapy due to a lessened concern about poor longer-term outcomes resulting from persistent uncontrolled blood glucose. Conversely, older patients may be more concerned about impending ill health, and thus be more likely to adhere to therapy.

Patients receiving 12 or more dispensings were 55% percent less likely to be non-adherent for MPR thresholds of 8:10 and 9:10 days. However, our calculations of total dispensings do not equate to the total number of medications prescribed, since non-adherence and differing days supply of medications may be responsible for some portion of the difference in the number of dispensings. Nevertheless, patients that received less than 12 dispensings were more likely to be identified as having an MPR below 8:10 and 9:10 days. A possible explanation for this finding is that patients receiving less than 12 dispensings during the four-month period were less ill, and

perhaps less adherent for reasons related to the health beliefs model as previously described. Also, it is likely that patients receiving 12 or more dispensings were afflicted with other co-morbid conditions and thus more vigilant in their adherence to therapy in an effort to stave off ill health.

Removing the term for the total number of prescriptions from multivariate models resulted in a decrease in the odds of non-adherence among patients dispensed both a sulfonylurea and metformin. Thus, controlling for the number of prescriptions dispensed resulted in an increase in the odds for non-adherence among those prescribed both drugs. Such effect was lacking for all other independent variables except age. Gender and insurance type were not found to be significant influences of medication possession.

Depression was identified as a risk factor for non-adherence by DiMatteo (34). In an attempt to control for the presence of depression, we identified patients that received a dispensing for one of several anti-depressant medications. For such patients, the risk of nonadherence to drug therapy was greater. However, the 95% confidence interval did not exclude the possibility that no effect was present (MPR < 8:10: 95% CI 0.92 – 1.75; MPR < 9:10: 95% CI 0.89 – 1.64). Additionally, dispensing of an anti-depressant was not found to be a significant influence of medication possession in multivariate models that included all potential confounding variables. Thus, in this study, patients who

received one or more selected antidepressant medications were not more likely to be nonadherent to hypoglycemic drug therapy.

An important limitation of the study relates to the use of medication possession as a measure of adherence. Certainly the possession of medication is only an initial step in the process of adhering to prescribed therapy. Patients in possession of medication may skip dosages when feeling well, or otherwise consume medication in a manner that differs from the instructions of the prescriber. Despite this limitation, possession of medication has been considered a useful 'first-order' measure of adherence (60), since patients must first possess medication before they can adhere to therapy.

Another limitation relates to the duration of time used to assess medication possession. The four-month period used in this study is shorter than what was used to assess adherence to hypoglycemic drug regimens for some other studies. For example, Morris used a three-year period to investigate hypoglycemic drug dispensings (47), while both Skaer at al (53) and Sclar at al (46) assessed refill dispensings over a 12-month period. Beta-Brown et al (61) investigated hypoglycemic drug use over a ten-year period. In our study, use of a longer period of time for assessing adherence would have likely resulted in a greater number of patients identified as non-adherent. It cannot be assumed that such patients would have been similarly distributed in terms

of regimen type and medication possession. Thus, a longer period of time used to assess medication possession may have resulted in different findings.

Additionally, patients receiving dual therapy may have initially failed monotherapy due to poor adherence. Thus, the group of patients using two hypoglycemic medications may inherently be more likely to be nonadherent.

Importantly, this study did not include many important factors known to be associated with adherence to prescribed drug regimens. Though we assessed the influence of gender and age, other patient-related factors may have been important to include. For example, race may have been an influence on adherence with sulfonylurea treatment, as found by Sclar et al (46). More notably, other complex behavioral factors may have been responsible for the differences in medication possession observed. For example, a patient's self-efficacy in adhering to prescribed regimens has been associated with superior adherence (29). Additionally, a patient's stage of readiness to adhere to a prescribed regimen may prove explanatory (62, 63). In this study, the identification and incorporation of factors related to perception and beliefs may have influenced the association between drug regimen type and medication possession.

Additionally, important factors related to the characteristics of the disease were not included in this analysis. It is possible, for example, that some

patients classified as non-adherent in fact no longer required medication, perhaps from adherence to recommended diet or exercise programs. Also, a percentage of patients classified as non-adherent may have been hospitalized during the assessment period. Additionally, the severity of disease may have also been important to assess, as highly symptomatic patients may have been more likely to adhere to therapy. Severity of disease may partly explain the finding of increased medication possession among older patients.

Other potentially important confounding factors relate to obtaining medication. Information related to prescription co-payment was not provided, thus the influence of out-of-pocket expenditure on medication possession cannot be assessed. Additionally, though patients were required to obtain prescriptions at designated pharmacies for reimbursement, it is possible that some patients filled prescriptions at other locations by using other insurances or by paying cash. A last potentially important factor related to the drug regimen not included in this analysis relates to the type of drug therapies studied. Though sulfonylureas and metformin remain popular therapies in the treatment of type 2 diabetes, newer hypoglycemic agents have become increasingly utilized during the past several years. Though dual therapy with a sulfonylurea plus metformin was found to be associated with an increased likelihood of non-adherence, the association between other hypoglycemic drug combinations and medication possession is uncertain. One must not assume that adherence to therapy would also be lesser for combination therapies that

include, for example, a thiazoladinedionne, meglitinde, or alpha glucosidase inhibitor.

Finally, it is important to note that dose frequency was not included as an influence on medication possession. Both metformin and sulfonylureas may be prescribed as one or two daily doses; depending upon the agent prescribed for the latter. (64). A sustained release preparation of metformin was not available during the period of study.

Despite these limitations, we found that patients receiving dispensings for both a sulfonylurea and metformin possessed medication for a lesser number of days as compared with patients who were dispensed only a sulfonylurea or metformin. This effect was strongest when controlling for the age of the patients and the total number of prescription dispensings. In this model, patients who received dispensings for both drugs were 3.14 times more likely to be non-adherent as defined as possessing medication for less than 8 of 10 days in the measurement period. Such patients were also 3.20 times more likely to be non-adherent using an MPR threshold of 9 in 10 days. The association between dual therapy with sulfonylurea plus metformin and an MPR of less than 8:10 or 9:10 was also significant in bivariate analyses.

Adherence with drug therapy was found to be sub-optimal among all patients, regardless of regimen type. Greater than one in four of all patients did not

possess a sufficient quantify of medication to adhere to prescribed therapy at least 80% of days; and roughly two in five patients did not possess enough medication to adhere to therapy at least 90% of days. Additionally, these estimates likely underestimate the true rate of adherence, since possessing medication is but one step in the process of adherence.

Despite the limitations described, this research should add to evidence demonstrating that adherence to hypoglycemic drug therapy is a fundamental problem, and potentially the greatest influence on the development of diabetic complications. Accordingly, adherence to drug therapy for patients with diabetes deserves at least as much attention as other components of diabetes management, such as preventative exams and monitoring of blood pressure and lipid levels.

## CONCLUSION

As compared with monotherapy with a sulfonylurea or metformin, dual therapy with a sulfonylurea plus metformin is associated with a greater than three fold increase in the likelihood of non-adherence, controlling for the age of the patient and total number of medications dispensed. Patients receiving monotherapy with sulfonylurea were most frequently adherent, with 77% of patients possessing medication for at least 8 of 10 days in the study period, and 67% receiving at least enough medication to cover 9 of 10 days. Of those receiving monotherapy with metformin, 77% possessed enough medication to adhere 8 of 10 days, and 57% of patients possessed enough medication to adhere 9 of 10 days. The lowest rate of adherence was among patients receiving dispensings for a sulfonylurea and metformin. Among patients receiving both drugs, 57% received enough medication to adhere 8 of 10 days, while only 43% of patients possessed at least enough medication for 9 of 10 days.

In this population many patients did not adhere to drug therapy to the extent considered necessary to achieve tight glycemic control. Such patients can be expected to be at increased risk for several types of diabetic complications. Thus, components of diabetes management must include the assessment of adherence with prescribed hypoglycemic drug regimens, and the application of interventions known to be effective in improving adherence. Additionally, the

complexity of the drug regimen should be considered as a potential barrier to optimal adherence.

**Table 1. Medications Used to Identify Patients as Having Received an Anti-Depressant Medication.**

| SSRI | Other |
|---|---|
| Citalopram | Bupropion |
| Fluoxetine | Mirzatapine |
| Paroxetine | Nefazodone |
| Sertraline | Trazodone |
| | Venlafaxine |

**Table 2. Characteristics of Patients Receiving Hypoglycemic Therapy with a Sulfonylurea and/or Metformin**

| | Sulfonylurea (N = 967; 62.9%) | | Metformin (N = 166; 10.8%) | | Sulfonylurea + Metformin (N = 404; 26.3%) | | Total Population (N = 1537) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Gender | | | | | | | | |
| Male | 572 | 59.15 | 85 | 51.20 | 215 | 53.22 | 872 | 56.73 |
| Female | 395 | 40.85 | 81 | 48.80 | 189 | 46.78 | 665 | 43.27 |
| Age | | | | | | | | |
| under 50 | 229 | 23.68 | 55 | 33.13 | 104 | 25.74 | 388 | 25.24 |
| 50-64 | 442 | 45.71 | 81 | 48.80 | 202 | 50.00 | 725 | 47.17 |
| 65 + | 296 | 30.61 | 30 | 18.07 | 98 | 24.26 | 424 | 27.59 |
| Insurance | | | | | | | | |
| Plan A | 315 | 32.57 | 53 | 31.93 | 114 | 28.22 | 482 | 31.36 |
| Plan B | 527 | 54.50 | 95 | 57.23 | 246 | 60.89 | 868 | 56.47 |
| Other | 125 | 12.93 | 18 | 10.84 | 44 | 10.89 | 187 | 12.17 |
| # of Dis-pensings | | | | | | | | |
| under 5 | 151 | 15.62 | 31 | 18.67 | 3 | 0.74 | 185 | 12.04 |
| 5-15 | 550 | 56.88 | 95 | 57.23 | 213 | 52.72 | 858 | 55.82 |
| over 15 | 266 | 27.51 | 40 | 24.10 | 188 | 46.53 | 494 | 32.14 |
| Rx for Depression | 105 | 10.86 | 22 | 13.25 | 66 | 16.34 | 193 | 12.56 |

**Table 3. Medication Possession: Patients Receiving Dispensings for Sulfonylurea and/or Metformin, and Total Population**

| | Sulfonylurea (n = 967) | | Metformin (n = 166) | | Sulfonylurea + Metformin (n = 404) | | Total Population (N = 1537) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Medication Possession Ratio (MPR) | | | | | | | | |
| >= 8:10 | 747 | 77.2 | 118 | 71.1 | 230 | 56.93 | 1095 | 71.24 |
| >= 9:10 | 646 | 66.8 | 94 | 56.6 | 174 | 43.07 | 914 | 59.47 |

**Table 4a: Bivariate Analyses: Medication Possession Ratio (MPR) and Gender, Age Category, Insurance Type, Number of Prescriptions Dispensed, and Rx for Depression**

MPR < 8:10

| | Sulfonylurea n = 967 % | Metformin n = 166 % | Sulfonylurea plus Metformin n = 404 % | Total population n = 1537 % |
|---|---|---|---|---|
| All Subjects | 22.75 | 28.92 | 43.07 | 28.76 |
| Regimen type | | | | |
| sfu or Met | - | - | - | 23.65** |
| sfu + Met | - | - | - | 43.07** |
| Gender | | | | |
| Male | 22.72 | 29.41 | 44.65 | 28.78 |
| Female | 22.78 | 28.40 | 41.27 | 28.72 |
| Age | | | | |
| Under 50 | 33.19** | 36.36 | 53.85* | 39.18** |
| 50-64 | 19.46** | 27.16 | 40.59* | 26.21** |
| 65 or older | 19.59** | 20.00 | 36.73* | 23.58** |
| Insurance | | | | |
| Plan A | 24.80 | 33.33 | 40.35 | 26.76 |
| Plan B | 20.95 | 32.08 | 43.90 | 29.49 |
| Other | 23.34 | 26.32 | 45.45 | 30.48 |
| # of Dis-pensings | | | | |
| < 5 | 41.72** | 45.16 | - | 43.24** |
| 5-15 | 22.00** | 26.32 | 53.99 | 30.42** |
| > 15 | 13.53** | 22.50 | 29.79† | 20.45** |
| Rx for depression | | | | |
| Yes | 30.48* | 31.82 | 37.89 | 33.16 |
| No | 21.81* | 28.47 | 44.08 | 28.13 |

* $p < 0.05$
** $p < 0.01$

†Not reportable; one cell with less then 5 subjects

**Table 4b: Bivariate Analyses: Medication Possession Ratio (MPR) and Gender, Age Category, Insurance Type, Number of Prescriptions Dispensed, and Rx for Depression**

MPR < 9:10

| | Sulfonylurea n = 967 % | Metformin n = 166 % | Sulfonylurea plus Metformin n = 404 % | Total population n = 1537 % |
|---|---|---|---|---|
| All subjects | 33.2 | 43.4 | 56.93 | 59.47 |
| Regimen type | | | | |
| sfu or Met | - | - | - | 34.69** |
| sfu + Met | - | - | - | 56.93** |
| Gender | | | | |
| Male | 33.57 | 44.71 | 59.07 | 40.94 |
| Female | 32.66 | 41.98 | 54.50 | 40.00 |
| Age | | | | |
| Under 50 | 43.23** | 52.73 | 64.42 | 50.26** |
| 50-64 | 29.19** | 39.51 | 54.95 | 37.52** |
| 65 or older | 31.42** | 36.67 | 53.06 | 36.79** |
| Insurance | | | | |
| Plan A | 32.06 | 43.40 | 54.39 | 38.59 |
| Plan B | 32.64 | 41.05 | 56.50 | 40.32 |
| Other | 38.40 | 55.56 | 65.91 | 46.52 |
| # of Dis-pensings | | | | |
| < 5 | 54.97** | 61.29 | - | 56.76** |
| 5-15 | 34.00** | 41.05 | 67.61 | 43.13** |
| > 15 | 19.17** | 35.00 | 44.15† | 29.96** |
| Rx for depression | | | | |
| Yes | 41.90* | 40.91 | 50.00 | 44.56 |
| No | 32.13* | 43.75 | 58.28 | 39.96 |

* $p < 0.05$
** $p < 0.01$
†Not reportable; one cell with less then 5 subjects

**Table 5a. Bivariate Logistic Regression Models: Independent Variables and MPR < 8:10**

| | ß | se | OR | 95% CI low | 95% CI high |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 0.8929 | 0.0699 | 2.442 | 1.921 | 3.104 |
| Age | | | | | |
| Under 50* | | | 1.0 | | |
| 50-65 | -0.5955 | 0.1340 | 0.551 | 0.424 | 0.717 |
| 65 + | -0.7357 | 0.1546 | 0.479 | 0.354 | 0.649 |
| Male gender | 0.0031 | 0.1138 | 1.003 | 0.810 | 1.254 |
| Number of dispensings | | | | | |
| 12 + | -0.5731 | 0.1142 | 0.564 | 0.451 | 0.705 |
| Insurance | | | | | |
| Plan A | | | 1.0 | | |
| Plan B | 0.1351 | 0.1270 | 1.145 | 0.892 | 1.468 |
| Other insurance | 0.1822 | 0.1893 | 1.2 | 0.828 | 1.739 |
| Rx for anti-depressant | 0.2374 | 0.1645 | 1.268 | 0.918 | 1.750 |

† versus monotherapy

**Table 5b. Bivariate Logistic Regression Models: Independent Variables and MPR < 9:10**

| | ß | se | OR | 95% CI low | 95% CI high |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 0.9118 | 0.1183 | 2.489 | 1.974 | 3.138 |
| Age | | | | | |
| Under 50* | | | 1.0 | | |
| 50-65 | -0.5204 | 0.1273 | 0.594 | 0.463 | 0.763 |
| 65 + | -0.5514 | 0.1430 | 0.576 | 0.435 | 0.763 |
| Male gender | 0.0390 | 0.1049 | 1.040 | 0.847 | 1.277 |
| Number of dispensings | | | | | |
| 12 + | -0.5562 | 0.1049 | 0.573 | 0.467 | 0.704 |
| Insurance | | | | | |
| Plan A | | | 1.0 | | |
| Plan B | 0.0726 | 0.1164 | 1.075 | 0.856 | 1.351 |
| Other insurance | 0.3254 | 0.1739 | 1.385 | 0.985 | 1.947 |
| Rx for anti-depressant | 0.1888 | 0.1552 | 1.208 | 0.891 | 1.637 |

† versus monotherapy

**Table 6. Likelihood Ratio Test for 2-Way Interactions**

| DV | | -2log statistic | -2log difference | $X^2_{df=26}$: 40.11 |
|---|---|---|---|---|
| MPR < 8:10 | EV + V's* | 1693.107 | | |
| | V's* | 1720.317 | 27.21 | NS |
| MPR< 9:10 | EV + V's* | 1912.485 | | |
| | V's* | 1941.272 | 28.79 | NS |

* EV = Interaction terms; V = Single terms (independent variables)

**Table 7a. Multivariate Logistic Model, All Independent Variables**

MPR < 8:10

| | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 1.1382 | 0.1339 | 3.121 | 2.401 | 4.058 |
| Age | | | | | |
| under50 | | | 1.00 | | |
| 50-64 | -0.5226 | 0.1398 | 0.593 | 0.451 | 0.780 |
| 65+ | -0.5557 | 0.1616 | 0.574 | 0.418 | 0.787 |
| Male Gender | -0.0405 | 0.1205 | 0.960 | 0.758 | 1.216 |
| Insurance | | | | | |
| Plan A | | | 1.00 | | |
| Plan B | 0.0107 | 0.1331 | 1.011 | 0.779 | 1.312 |
| Other | 0.0759 | 0.1970 | 1.079 | 0.733 | 1.587 |
| # of Dis-pensings | | | | | |
| 12 + | -0.8309 | 0.1297 | 0.436 | 0.338 | 0.562 |
| Rx for Anti-depressant | 0.3040 | 0.1778 | 1.355 | 0.956 | 1.920 |

† versus monotherapy

**Table 7b. Multivariate Logistic Model, All Independent Variables**

MPR < 9:10

| | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 1.1634 | 0.1284 | 3.201 | 2.489 | 4.117 |
| Age | | | | | |
| under50 | | | 1.00 | | |
| 50-64 | -0.4463 | 0.1331 | 0.640 | 0.493 | 0.831 |
| 65+ | -0.3721 | 0.1503 | 0.689 | 0.513 | 0.925 |
| Male Gender | 0.00125 | 0.1112 | 1.001 | 0.811 | 1.245 |
| Insurance | | | | | |
| Plan A | | | 1.00 | | |
| Plan B | -0.0393 | 0.1221 | 0.962 | 0.757 | 1.222 |
| Other | 0.2328 | 0.1813 | 1.262 | 0.885 | 1.801 |
| # of Dis-pensings | | | | | |
| 12 + | -0.8108 | 0.1186 | 0.445 | 0.352 | 0.561 |
| Rx for Anti-depressant | 0.2697 | 0.1674 | 1.310 | 0.943 | 1.818 |

† versus monotherapy

**Table 8a. Multivariate Logistic Model: Type of Drug Therapy, Age Category, and Number of Dispensings**

MPR < 8:10

| | Beta | se | OR | 95 % CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 1.1442 | 0.1334 | 3.140 | 2.417 | 4.078 |
| Age | | | | | |
| under50 | | | 1.000 | | |
| 50-64 | -0.5392 | 0.1392 | 0.583 | 0.444 | 0.766 |
| 65+ | -0.5679 | 0.1609 | 0.567 | 0.413 | 0.777 |
| # of Dis-pensings | | | | | |
| 12 + | -0.7937 | 0.1266 | 0.452 | 0.353 | 0.580 |

† versus monotherapy

**Table 8b.Multivariate Logistic Model: Type of Drug Therapy, Age category, and Number of Dispensings**

MPR < 9:10

| | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 1.1621 | 0.1279 | 3.197 | 2.488 | 4.108 |
| Age | | | | | |
| under50 | | | 1.000 | | |
| 50-64 | -0.4586 | 0.1325 | 0.632 | 0.488 | 0.820 |
| 65+ | -0.3743 | 0.1496 | 0.688 | 0.513 | 0.922 |
| # of Dis-pensings | | | | | |
| 12 + | -0.7886 | 0.1159 | 0.454 | 0.362 | 0.570 |

† versus monotherapy

**Table 9a.Multivariate Logistic Model: Type of Drug Therapy and Age Category**

MPR < 8:10

| | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 9:1021 | 0.1239 | 2.465 | 1.933 | 3.142 |
| Age | | | | | |
| under50 | | | 1.000 | | |
| 50-64 | -0.6293 | 0.1369 | 0.533 | 0.408 | 0.697 |
| 65+ | -0.7266 | 0.1574 | 0.484 | 0.355 | 0.658 |

† versus monotherapy

**Table 9b.Multivariate Logistic Model: Type of Drug Therapy and Age category**

MPR < 9:10

| | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| Dispensed sulfonylurea plus metformin† | 0.9215 | 0.1193 | 2.513 | 1.989 | 3.175 |
| Age | | | | | |
| under50 | | | 1.000 | | |
| 50-64 | -0.5528 | 0.1301 | 0.575 | 0.446 | 0.742 |
| 65+ | -0.5383 | 0.1458 | 0.584 | 0.439 | 0.777 |

† versus monotherapy

**Table 10a. Association Between Dual Therapy With a Sulfonylurea Plus Metformin† and Medication Possession: Comparison of Logistic Models**

MPR < 8:10

| Model | Beta | se | OR | 95% CI low | 95% CI High |
|---|---|---|---|---|---|
| 1 | 1.1382 | 0.1339 | 3.121 | 2.104 | 4.058 |
| 2 | 1.1442 | 0.1334 | 3.140 | 2.417 | 4.078 |
| 3 | 9:1021 | 0.1239 | 2.465 | 1.933 | 3.142 |
| 4 | 0.8929 | 0.0699 | 2.442 | 1.921 | 3.104 |

| | Additional Variables |
|---|---|
| Model 1 | All independent variables (from Table 7a) |
| Model 2 | Age category and number of dispensings (from Table 8a) |
| Model 3 | Age category only (from Table 9a) |
| Model 4 | No additional variables: bivariate relationship (from Table 5a) |

† versus monotherapy

**Table 10b. Association Between Dual Therapy With a Sulfonylurea Plus Metformin† and Medication Possession: Comparison of Logistic Models**

MPR < 9:10

| Model | Beta | se | OR | CI low | CI High |
|---|---|---|---|---|---|
| 1 | 1.1634 | 0.1284 | 3.201 | 2.489 | 4.117 |
| 2 | 1.1621 | 0.1279 | 3.197 | 2.488 | 4.108 |
| 3 | 0.9215 | 0.1193 | 2.513 | 1.989 | 3.175 |
| 4 | 0.9118 | 0.1183 | 2.489 | 1.974 | 3.138 |

| | Additional Variables |
|---|---|
| Model 1 | All independent variables (from Table 7b) |
| Model 2 | Age category and number of dispensings (from Table 8b) |
| Model 3 | Age category only (from Table 9b) |
| Model 4 | Bivariate relationship (from Table 5b) |

† versus monotherapy

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# PART 2

Part 2 includes the following appendices:

Appendix A. Background and Review of the Problem

Appendix B. Details of the Methods

Appendix C. Overview of Major Findings

## Appendix A. Background and Review of the Problem

Diabetes is a major public health problem. According to data from the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of diabetes in 1988-1994 was estimated to be slightly greater than five percent for Americans 20 years of age or older (1). The prevalence of diabetes was also found to be greater for certain races, with the condition being increasingly prevalent among Mexican-Americans (5.6%) and non-Hispanic blacks (6.9%). Additionally, applying criteria developed by the American Diabetes Association to NHANES III data, another 2.7% of the U.S. population have diabetes yet are undiagnosed (2).

The prevalence of diabetes has increased during the past three decades, and this trend is projected to continue (3). Major factors contributing to the increase in diabetes prevalence include the aging of the U.S. population and an increased prevalence rate of diabetes among older Americans (4, 5). Additionally, diabetes-related deaths have decreased during past several decades, likely resulting from advances in knowledge and related improvements in diabetes care (1). Poor diet and sedentary lifestyles have also contributed to the increase in diabetes prevalence, with obesity and lack of exercise often present as characteristics of the diabetic patient (6). Diabetes will likely continue to be a significant epidemiologic problem in coming years, as the number of older Americans continues to increase.

Further, a growing number of Americans are obese (7), work environments increasingly involve prolonged sedentary activity, and burdensome demands associated with current lifestyles can make it difficult to incorporate healthy nutrition and exercise into one's daily routine.

Though diabetes has emerged as an important public health problem, strides in treatment have resulted in reduced morbidity. The Diabetes Control and Complications Trial (DCCT) (8) demonstrated that intensive therapy in type 1 diabetes can reduce the incidence of retinopathy, neuropathy, and nephropathy. In this trial, intensive therapy was defined as three or more daily insulin injections guided by frequent blood glucose monitoring. The DCCT demonstrated for the first time that aggressive management can reduce the risk of some types of diabetic complications (9). Five years later, similar results were reported from a large trial investigating the effect of intensive glucose control among British patients with type 2 diabetes. The United Kingdom Prospective Diabetes Study Group (10) assessed the effects of tight control of blood glucose, using an intensive drug regimen aimed at achieving a fasting plasma glucose concentration of a less than 6 mmol/L. As compared to patients who received a regimen consisting of conventional care, those receiving intensive therapy were 25% less likely to be diagnosed with a microvascular complication, and 12% less likely to suffer any diabetes-related endpoint. The DCCT and UKPDS studies were important in demonstrating that several types of diabetic complications can be averted through tight

control of blood glucose. Additional trials have since reported similar findings. Examples include the Kumamoto Study in Japan (11) and the Veteran's Affairs Cooperative Study on Glycemic Control and Complications (12), which both reported reductions in risk for selected microvascular diseases among patients receiving intensive therapy.

Intensive therapy has not been shown to significantly reduce the incidence of macrovascular diseases such as myocardial infarction or stoke. Though a trend for a reduction in these endpoints was observed among those receiving intensive therapy in the UKPDS, the frequency of such events was substantially greater than the frequency of microvascular complications (13). Thus, though the UKPDS trial was sufficiently powered to detect a statistically significant reduction in macrovascular complications, no such reduction was observed. Additional information regarding the association between regimens of tight control and macrovascular disease will be provided from the ongoing Veteran's Affairs Diabetes Trial (14), which is assessing the effect of intensive blood glucose control on cardiovascular complications in patients with type 2 disease. Meanwhile, current evidence suggests that control of blood glucose alone is not sufficient to significantly reduce the incidence of heart attack, stroke, or diabetes-related death. Aggressive management of other cardiovascular risk factors is essential, including reduction of LDL-C cholesterol and blood pressure to below target levels (15).

Strategies for achieving tight glycemic control include hypoglycemic drug therapy, though no single class of oral hypoglycemic medication has demonstrated superior ability in achieving tight control. In the UKPDS trial, patients assigned to intensive therapy with oral medication initially received either a first or second-generation sulfonylurea. Patients failing sulfonylurea monotherapy received insulin injections, or metformin if overweight (16). No single agent or class of agents was associated with superior outcomes. All hypoglycemic medications utilized were efficacious in reducing blood glucose, yet the specific agent used to achieve this reduction was not of importance. Current treatment guidelines of the American Diabetes Association describe the goal HbA1c to be achieved, yet do not recommend specific agents for achieving this goal (17).

During the past several years, three new classes of oral hypoglycemic drugs have become available for use. None of these newer classes of hypoglycemic agents has been proven superior in reducing the incidence of microvascular or macrovascular diabetic complications. However, the availability of newer classes of hypoglycemic drugs has created a panoply of choices for achieving euglycemia. Currently, prescribers can chose from over 25 different agents representing five different classes of oral hypoglycemic drugs (18). Some of these agents can be utilized as monotherapy (19, 20); most have been approved for use in combination with other hypoglycemic medications (19-25).

The first objective of this research project was to describe hypoglycemic drug utilization in a diabetic population. In this descriptive study, we sought to identify which mediations were utilized and how frequently they were dispensed both alone and in combination. We also identified patients that switched hypoglycemic regimens during a 12-month period, and identified to which regimens patients were switching. We also compared utilization by age, gender, and insurance type, including a comparison of the costs associated with hypoglycemic drug utilization. This study will be of particular interest to those seeking details of 'real-world' patterns of hypoglycemic drug utilization, and how drug utilization varies among sub-populations.

Recognizing the reductions in several types of diabetic complications observed among patients receiving intensive therapy in the DCCT and UKPDS trials, we also explored the relationship between adherence to prescribed regimens and changes in drugs dispensed. Specifically, we hypothesized that patients that did not consistently receive dispensings for prescribed hypoglycemic medications would be more likely to receive a higher dose of hypoglycemic medication or a dispensing for a different (new) hypoglycemic medication in subsequent months. Thus, we attempted to demonstrate that in patients who were nonadherent to prescribed regimens, prescribers might have responded to resulting poor control of blood glucose by prescribing additional medication. This action may potentially provoke dangerous hypoglycemia. Further, it fails to address the behavior of nonadherence to

prescribed hypoglycemic therapy, which may ultimately result in diabetic complications that could have been avoided.

A third study involved assessing adherence with drug therapy among patients prescribed monotherapy with a sulfonylurea or metformin, and among patients prescribed dual therapy with both agents. We hypothesized that patients prescribed dual therapy would be less adherent that those prescribed monotherapy, and that adherence to hypoglycemic drug regimens would be less than optimal overall. This hypothesis was based upon the findings of other researchers who have reported poor adherence with therapies for chronic diseases (26-31). Adherence with prescribed drug therapy in diabetes is an acknowledged problem, and many have reported adherence rates that would seem to fail to be consistent with requirements for tight control of blood glucose (32-34). Morris et al (35) specifically examined the difference in adherence between patients receiving monotherapy with a sulfonylurea or metformin as compared with patients receiving dual therapy with both agents. In a presentation at the American Diabetes Association's 60$^{th}$ Annual Scientific Session, Morris reported that a significant difference in adherence was observed among those prescribed both a sulfonylurea and metformin, and that a far less than optimal rate of adherence existed among those receiving hypoglycemic monotherapy. In third study presented here, we assessed adherence among regimen types, focusing on the likelihood of nonadherence among patients receiving dual therapy.

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## Appendix B Details of the Methods

### Data source

Data for research were provided by Consumer Value Stores (CVS), Inc to the department of Applied Pharmaceutical Sciences at the University of Rhode Island. The data consisted of a population of enrollees in a comprehensive management program for diabetic patients sponsored by either of two area health insurance providers. The initial data set included 288,174 medication dispensings to 5056 patients between April 27,1997 and May 16,1999. The data included the following 16 variables:

**ID:** Patient Identification number; a unique integer from 1 to 5056.

**BDATE:** Patient date of birth; in *mm/dd/yyyy* format.

**GENDER**: Male or Female, included as 'M' or 'F'.

**AGENCYNM:** Describes the type of payment associated with the medication dispensing. For a majority of patients, this variable was one of two health plans participating in the diabetes management program. Other insurance types used for prescription reimbursement and cash payments were described by this variable.

**AGENCYID:** Numeric descriptor for above

**RX_NBR:** Unique number assigned by the dispensing pharmacy for each new prescription dispensed and associated refills.

**FILL_NBR:** Identifies the refill number

**NDC:** National Drug Code identifier; a unique identification number used for identifying the product dispensed.

**LABELNM:** Name of the product dispensed, including strength and dosage from.

**QTY:** The quantity of medication dispensed

**DAYSSUPP:** The days supply of medication dispensed

**AWPPRICE:** The average wholesale price of the quantity of product dispensed on the date of dispensing.

**POSTXNDT:** The date on which the medication was dispensed to the patient or his/her agent

**AVAILFIL:** The number of refills remaining on the prescription

**STORENO:** The store number, a unique identifier for the pharmacy dispensing the medication

**DEA**: A unique identification number assigned to providers and institutions

**Data cleaning and preparation**

Data was provided in comma-delimited form. From this file, a SAS data set was created using SAS for microcomputers versions 6.2 and 8.01. SAS procedures such as PROC FREQ and PROC UNIVARIATE were used to screen for missing and spurious data. Five duplicate records were deleted. The resulting data set described 288,171 medication dispensings. Missing values for the date of dispensing (POSTXNDT) were present for 5470 of these observations (1.9%), and were considered to represent prescriptions held 'on-file' in the computer system. Such observations were deleted, further reducing the number of dispensings to 282,701.

A next step was to create a date set that included only dispensings for hypoglycemic medications. The PROC FREQ procedure was used to identify all medications dispensed. Using this output, text strings describing hypoglycemic products were identified and incorporated into a SAS program that deleted dispensings for drugs not used for blood glucose control. A total of 671 patients did not receive a dispensing for a hypoglycemic medication (13.3%): these patients were eliminated from the sample. The resulting data set included only patients that received dispensings for a hypoglycemic medication (N = 4385), and included only dispensings for hypoglycemic medications (n = 78,960).

The variable LABLENM was used to create two new variables for describing categories of hypoglycemic medication dispensed. The first such variable, RXCODE, consisted of the first four letters of the chemical name of the product dispensed plus the medication strength. For example, a label name of 'GLYBURIDE 5MG TABLET' was converted to 'glyb5'. Similarly, a dispensing for Diabeta® brand of glyburide 5mg was also coded as 'glyb5'. The use of the RXCODE variable facilitated categorization of dispensings by therapeutic class. The RXCODE drug categorization system was also useful in that a change in manufacturer of a product dispensed would not be categorized as a change in type of medication dispensed. Table 2 presents the description for variable LABLENM for all hypoglycemic drugs identified, and associated created variable RXCODE. A second variable, STRENGTH, was created to describe the strength of medication dispensed. An additional variable BRAND described the type of sulfonylurea dispensed as either brand or generic. Variables RXCODE, STRENGTH, and BRAND were created using if-then statements for each of 48 different descriptions of oral drugs described by variable LABELNM. All insulin products were coded as RXCODE 'ins' and STRENGTH '99999'.

Data was transposed to create a data set containing one record per patient, using the PROC TRANSPOSE procedure. The resulting data set included 4385 observations (subjects) and 772 variables.

To provide a standard for comparison, we included only patients that received dispensings of hypoglycemic medication for at least a 12-month period. This was accomplished by comparing the date of the first dispensing of hypoglycemic medication with the last date of dispensing. Patients with at least 365 days between first and last were included in the sample. The resulting data set included 2901 patients, representing 57.4% of the original 5056 subjects.

**Categorization of age, insurance type, and number of dispensings**

Using the variable BDATE, we created three age categories: under 50, 50-64, and greater than 65 years of age. These categories were established to compare drug utilization by younger, middle-aged, and senior diabetics. Such patients represented 35.54%, 43.40%, and 22.06% of the population respectively. In an effort to focus on patients with type 2 disease, we removed patients under 40 years of age from some analyses (age under 40: n = 386, 13.62% of total population).

For most patients (87.18%), the insurance type associated with hypoglycemic drug dispensings was one of two health plans. Of the remaining patients, 8.62% received dispensings that were reimbursed by one of over 50 other types of health insurance provider. Cash payment for dispensings was the sole insurance type associated with dispensings for 4.2% of subjects. In

comparisons of the drug regimen utilized, four categories of insurance type were identified: health plan A, health plan B, other insurance, and cash. For other bivariate and multivariate analyses, the insurance type categories of 'other insurance' and 'cash' were combined into a single category, since we were primarily interested in assessing differences between the two main health plans.

The total number of dispensings was a factor that included dispensings for any type of medication. The original data of all pharmacy dispensings was used to obtain values of this variable. To derive this variable, we first identified the earliest date of dispensing of a hypoglycemic medication. Next, we determined the number of dispensings for which the dispensing date was later than but no more than four months (122 days) following the first dispensing of a hypoglycemic medication. Univariate analysis of this variable was performed to obtain quartiles of the frequency distribution. The lowest, highest, and inner quartiles of frequency distribution were used to create the following three categories: under 5 dispensings; 5-15 dispensings, and greater than 15 dispensings.

**Creation of drug regimen categories**

The frequency of dispensing of hypoglycemic medications was assessed using the PROC FREQ procedure. Regimen categories were defined based

on dispensing frequencies and with a priori awareness of regimens of interest; such as users of sulfonylurea only and users of sulfonylurea plus metformin. To minimize misclassification resulting from changes in regimen during the 12-month period, we based drug regimen classification on the first three months of the 12-month period. Using the regimen categories presented in Figure 1, 98.3% of patients were classified as receiving one of nine types of hypoglycemic drugs regimen, with 1.72% of patients classified as receiving an 'other regimen'. The variable REGVAR was created, representing regimen categories 1-10. To assess changes in drug regimen during the 12-month period, we also categorized patients based upon the last three months of the 12-month period, using the same regimen classification strategy. The ten levels of variable ENDVAR represented the regimen category utilized during the last three months of the 12-month period.

**Identifying changes in regimen category and dose**

Changes in drug regimen utilized between the first and last three months of the 12-month period were identified by comparing values for variables REGVAR and ENDVAR. We also determined which regimens patients were switching to, presenting both the frequency and percentage of change.

We also identified changes in the dose of medication utilized. Two aspects of dispensings were assessed to determine if a change in dose had occurred.

First, a change in the variable RXCODE that did not result in a change in regimen category was considered to represent a change in medication dose. For example, a dispensing of glyburide 5mg tabs (RXCODE 'glyb5') was considered to represent a change in dose if previous dispensings were for glyburide 2.5mg tabs (RXCODE 'glyb2.5'). Second, we assessed the dose dispensed by comparing the number of doses per day. This was accomplished by dividing the quantity of medication dispensed by the days supply received. For example, a dispensing of 60 tablets for a supply of 30 days would be identified as a daily dose of 2. A difference in this value between dispensings of the same medication was considered to indicate a dose change. For analyses involving medication possession, patients were eliminated if either the drug dispensed or the daily dose differed during the first four months of the 12-month period.

**Determining the medication possession ratio**

The assessment of medication possession was based upon the first four months of the 12-month period. We calculated the total days supply of medication received for all dispensings preceding the last dispensing during the four-month period; and determined the total number of days between the first and last dispensing. The medication possession ratio (MPR) was defined as the total days supply of medication received compared with the total number of days between the first and last dispensing. Patients were

considered to be nonadherent if the MPR was less than 8:10, or less than 9:10 for some analyses. Patients who received only one dispensing during the four-month period but who received medication in subsequent months were classified as non-adherent.

**Analyses**

All analyses were performed using the variables described above, and using SAS for microcomputers version 8.01. The coding of variables and description of variable types is presented in Table 3. A summary of all analyses performed is presented in Tables 4a (univariate), 4b (bivariate), and 4c (multivariate).

Programming details were obtained from the SAS Procedures Guide (1) and the SAS Language and Procedures usage manual (2) . Fundamentals of SAS coding were learned using SAS Programming by Example by Cody and Pass (3). Interpretation of statistical procedures was aided by Hatcher and Stepanski's *A Step-by-Step Approach to Using the SAS System for Univariate and Multivariate Statistics* (4) and Allison's *Logistic Regression Using the SAS System* (5).

**Table 1. Drug Regimen Categories**

| | Regimen |
|---|---|
| 1 | Insulin only |
| 2 | Insulin + Troglitazone |
| 3 | Insulin + non-troglitazone agent |
| 4 | Sulfonylurea mono-therapy |
| 5 | Sulfonylurea + metformin |
| 6 | Sulfonylurea + non-metformin |
| 7 | Troglitazone mono-therapy |
| 8 | Glimepramide mono-therapy |
| 9 | Metformin mono-therapy |
| 10 | Other regimen not classified |

## Table 2. Variable LABELNM and Derived Variable RXCODE

| LABELNM | RXCODE |
|---|---|
| AMARYL 1MG TABLET | glim1 |
| AMARYL 2MG TABLET | glim2 |
| AMARYL 4MG TABLET | glim4 |
| CHLORPROPAMIDE 100MG TABLET | chlo100 |
| DIABETA 1.25MG TABLET | glyb1.2 |
| DIABETA 2.5MG TABLET | glyb2.5 |
| DIABETA 5MG TABLET | glyb5 |
| DIABINESE 100MG TABLET | chlo100 |
| DIABINESE 250MG TABLET | chlo250 |
| GLIPIZIDE 10MG TABLET | glip10 |
| GLIPIZIDE 5MG TABLET | glip5 |
| GLUCOPHAGE 1000MG TABLET | gluc100 |
| GLUCOPHAGE 500MG TABLET | gluc500 |
| GLUCOPHAGE 850MG TABLET | gluc850 |
| GLUCOTROL 10MG TABLET | glip10 |
| GLUCOTROL 5MG TABLET | glip5 |
| GLUCOTROL XL 10MG TABLET SA | glipxl1 |
| GLUCOTROL XL 5MG TABLET SA | glipxl5 |
| GLYBURIDE 1.25MG TABLET | glyb1.2 |
| GLYBURIDE 2.5MG TABLET | glyb2.5 |
| GLYBURIDE 5MG TABLET | glyb5 |
| GLYBURIDE MICRO 1.5MG TAB | glyb1.5 |
| GLYBURIDE MICRO 3MG TABLET | glyb1.5 |
| GLYBURIDE MICRO 6MG TABLET | glyb6 |
| GLYNASE 1.5MG PRESTAB | glyb1.5 |
| GLYNASE 3MG PRESTAB | glyb3 |
| GLYNASE 6MG PRESTAB | glyb6 |
| GLYSET 25MG TABLET | migl25 |
| GLYSET 50MG TABLET | migl50 |
| HUMALOG 100U/ML CARTRIDGE | ins |
| HUMALOG 100U/ML PEN | ins |
| HUMALOG 100U/ML VIAL | ins |
| HUMULIN 50/50 VIAL | ins |
| HUMULIN 70/30 CARTRIDGE | ins |
| HUMULIN 70/30 PEN | ins |
| HUMULIN 70/30 VIAL | ins |
| HUMULIN L 100U/ML VIAL | ins |
| HUMULIN N 100U/ML CARTRIDGE | ins |
| HUMULIN N 100U/ML PEN | ins |
| HUMULIN N 100U/ML VIAL | ins |
| HUMULIN R 100U/ML CARTRIDGE | ins |
| HUMULIN R 100U/ML VIAL | ins |
| HUMULIN R 500U/ML VIAL | ins |
| HUMULIN U 100U/ML VIAL | ins |
| MICRONASE 1.25MG TABLET | glyb1.2 |
| MICRONASE 2.5MG TABLET | glyb2.5 |
| MICRONASE 5MG TABLET | glyb5 |

**Table 2 (continued). Variable LABLENM and Derived Variable RXCODE**

| LABLENM | RXCODE |
|---|---|
| NOVOLIN 70/30 100U/ML VIAL | ins |
| NOVOLIN 70/30 150U/1.5ML PREFL | ins |
| NOVOLIN 70/30 U100 CARTRIDG | ins |
| NOVOLIN L 100U/ML VIAL | ins |
| NOVOLIN N 100U/ML CARTRIDGE | ins |
| NOVOLIN N 100U/ML SYRINGE | ins |
| NOVOLIN N 100U/ML VIAL | ins |
| NOVOLIN R 100U/ML CARTRIDGE | ins |
| NOVOLIN R 100U/ML SYRINGE | ins |
| NOVOLIN R 100U/ML VIAL | ins |
| NOVOPEN 1.5 INSULIN DEVICE | ins |
| NOVOPEN 3 INSULIN DEVICE | ins |
| ORINASE 500MG TABLET | tolb500 |
| PRANDIN 0.5MG TABLET | pran0.5 |
| PRANDIN 1MG TABLET | pran1 |
| PRANDIN 2MG TABLET | pran2 |
| PRECOSE 100MG TABLET | prec100 |
| PRECOSE 25MG TABLET | prec25 |
| PRECOSE 50MG TABLET | prec50 |
| REZULIN 200MG TABLET | rezu200 |
| REZULIN 300MG TABLET | rezu300 |
| REZULIN 400MG TABLET | rezu400 |
| TOLAZAMIDE 100MG TABLET | tola100 |
| TOLAZAMIDE 250MG TABLET | tola250 |
| TOLAZAMIDE 500MG TABLET | tola500 |
| TOLBUTAMIDE 500MG TABLET | tolb500 |
| TOLINASE 100MG TABLET | tola100 |
| TOLINASE 250MG TABLET | tola250 |

**Table 3. Coding of Variables Used in Analyses**

| Variable | Description (codified as) | Variable type |
|---|---|---|
| AGECAT | Under 50 (1); 50-64 (2); 65 or older (3) | categorical |
| AGECAT1 | Under 40 (1); 40-49 (2); 50-64 (3); 65 or older (4) | categorical |
| AGENCYNM | Insurer name (char) | character string |
| ANYCHANGE | Change in medication or dose or drug dispensed during the 12-month period (1); else (0) | dichotomous |
| AWP10 | The average wholesale price of the medication dispensed minus ten percent (num) | number |
| BDATE | Date of birth as SAS date (num) | continuous |
| BRAND | If brand product dispensed (1); generic (0) | dichotomous |
| CASH | Cash payment (1); else (0) | dichotomous (dummy) |
| COST12 | The 12 month cost of all hypoglycemic medication dispensed; calculated as AWP – 10% (num) | number |
| DAYSSUP | The days supply of medication dispensed (num) | integer |
| DEPRES | Received Rx for antidepressant (1); else (0) | dichotomous |
| DOSE | The quantity dispensed divided by the days supply (num) | number |
| DOSECHANGE | Change in dose of drug dispensed during the 12-month period (1); else (0) | dichotomous |
| ENDVAR | Category of drug regimen utilized (1-10), based on the last three months of dispensings; see Figure1, manuscript 1. | discrete |

| | | |
|---|---|---|
| FIRSTDT | Date of the earliest dispensing of a hypoglycemic medication (num) | SAS date |
| GEN1 | First generation sulfonylurea (1); else (0) | dichotomous |
| GENDER | Male (M) or female (F) | dichotomous |
| INSCAT | Insurance category: planA (1); planB (2); other insurance (3); cash (4) | categorical |
| LASTDT | Date of the latest dispensing of a hypoglycemic medication (num) | SAS date |
| MALE | Male (1); else (0) | dichotomous (dummy) |
| MEDCHANGE | Change in medication during the 12-month period (1); else (0) | dichotomous |
| MPR | Medication Possession Ratio; calculated by dividing quantity of medication dispensed by number of days between dispensings (num) | Continuous |
| MPR80 | If MPR < 0.80 then (1); else (0). | dichotomous |
| MPR90 | If MPR < 0.90 then (1); else (0). | dichotomous |
| OTHERINS | Other insurance (1); else (0) | dichotomous (dummy) |
| OTHINSCA | Other insurance or cash (1); else (0) | dichotomous (dummy) |
| OVER11 | Greater than 11 dispensings during first four months (1); else (0) | dichotomous (dummy) |
| OVER15 | Over 15 dispensings during first four months (1); else (0) | dichotomous (dummy) |
| OVER4LESS16 | Between 5 and 15 dispensings during first four months (1); else (0) | dichotomous (dummy) |
| OVER50UNDER65 | Age between 50-64 years (1); else (0) | dichotomous (dummy) |
| OVER65 | Age 65 years or older (1); else (0) | dichotomous (dummy) |

| | | |
|---|---|---|
| PLANA | Plan A (1); else (0) | dichotomous (dummy) |
| PLANB | Plan B (1); else (0) | dichotomous (dummy) |
| POSTXNDT | Date of dispensing (num) | SAS date |
| QTY | The quantity of medication dispensed (num) | integer |
| REGVAR | Category of drug regimen utilized (1-10), based on the first three months of dispensings; see Figure1, manuscript 1. | discrete |
| RXCODE | Used to identify class and strength of hypoglycemic medication dispensed (char) | character string |
| STRENGTH | Strength of medication dispensed; 9999 for insulin products (num) | number |
| TOTALRX | Total number of dispensings during first four months (num) | continuous (integer) |
| TROGLIT | Troglitazone dispensed (1); else (0) | dichotomous |
| TXTYPE | Dual therapy with both a sulfonylurea and metformin (1) or monotherapy with either agent (0) | dichotomous |
| UNDER5 | Less than 5 dispensings during first four months (1); else (0) | dichotomous (dummy) |
| UNDER50 | Age under 50 years (1); else (0) | dichotomous (dummy) |

**Table 4a. Summary of Univariate Analyses Performed**

IV = Independent Variable
DV = Dependent Variable
MPR = Medication Possession Ratio

| Population | Description | Procedure | Table #; (manuscript #) |
|---|---|---|---|
| All patients receiving dispensing s of hypo-glycemic drugs | Frequency and percent of patients for each age category | PROC FREQ | Table 1 (1) |
| | Frequency and percent of patients for gender | PROC FREQ | Table 1 (1) |
| | Frequency and percent of patients for each category of insurance type | PROC FREQ | Table 1 (1) |
| Patients receiving sulfonylure a only | Frequency and percent of patients receiving insulin or oral hypoglycemic agents | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for each age category | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for gender | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for each category of insurance type | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for each category of number of dispensings | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients receiving an anti-depressant medication | PROC FREQ | Table 1 (3) |
| | Mean medication possession ratio (MPR) < 8:10, < 9:10 | PROC FREQ | Table 2 (2) |
| | Frequency and percent of patients having a medication possession ratio (MPR) < 8:10 or < 9:10 | PROC FREQ | Table 2 (2) |

| | | | |
|---|---|---|---|
| Patients receiving metformin only | Frequency and percent of patients for each age category | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for gender | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for each category of insurance type | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients for each category of number of dispensings | PROC FREQ | Table 1 (2) |
| | Frequency and percent of patients receiving an anti-depressant medication | PROC FREQ | Table 1 (3) |
| | Mean medication possession ratio (MPR) < 8:10, < 9:10 | PROC FREQ | Table 2 (2) |
| | Frequency and percent of patients having a medication possession ratio (MPR) < 8:10 or < 9:10 | PROC FREQ | Table 2 (2) |
| Patients receiving both sulfonylurea and metformin | Frequency and percent of patients for each age category | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for gender | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for each category of insurance type | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for each category of number of dispensings | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients receiving an anti-depressant medication | PROC FREQ | Table 1 (3) |
| Patients receiving sulfonylurea only or met-formin only | Frequency and percent of patients having a medication possession ratio (MPR) < 8:10 or < 9:10 | PROC FREQ | Table 2 (2) |

| | | | |
|---|---|---|---|
| All patients receiving sulfonylurea only or metformin only, or receiving both drugs | Frequency and percent of patients for each age category | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for gender | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for each category of insurance type | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients for each category of number of dispensings | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients receiving an anti-depressant medication | PROC FREQ | Table 1 (3) |
| | Frequency and percent of patients having a medication possession ratio (MPR) < 8:10 Or < 9:10 | PROC FREQ | Table 2 (2) |
| | Frequency and percent of patients having a medication possession ratio (MPR) >= 8:10 Or >= 9:10 | PROC FREQ | Table 2 (3) |

**Table 4b. Summary of Bivariate Analyses Performed**

| Population | Description | Procedure | Table #; (manuscript #) |
|---|---|---|---|
| All patients receiving dispensings of hypo-glycemic drugs (N = 29,001) | Drug regimen and Gender | Chi-Square | Table 4 (1) |
| | Drug regimen and age | Chi-Square | Table 5a (1) |
| | Drug regimen and insurance type | Chi-Square | Table 6 (1) |
| | Cost of medications dispensed and Age | ANOVA, Tukey's test | Table 9 (1) |
| | Cost of medications dispensed and Gender | Student's t-test | Table 9 (1) |
| | Cost of medications dispensed and Insurance type | ANOVA, Tukey's test | Table 9 (1) |
| Above, if patient >= 40 years of age | Drug regimen and Age | Chi-Square | Table 5b (1) |
| | Troglitazone dispensings and Age | Chi-Square | Table 8 (1) |
| Patients receiving sulfonylurea only | Brand name sulfonylurea and age | Chi-Square | Table 7 (1) |
| | Brand name sulfonylurea and gender | Chi-Square | Table 7 (1) |
| | Brand name sulfonylurea and insurance type | Chi-Square | Table 7 (1) |
| | Medication possession ratio (< 8:10) and age | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and gender | Chi-Square | Table 3 (2) |

| | | |
|---|---|---|
| Medication possession ratio (< 8:10) and insurance type | Chi-Square | Table 3 (2) |
| Medication possession ratio (< 8:10) and number of dispensings | Chi-Square | Table 3 (2) |
| Medication possession ratio (< 8:10) and dual drug therapy | Chi-Square | Table3a (3) |
| Medication possession ratio (< 8:10) and Rx for depression | Chi-Square | Table3a (3) |
| Medication possession ratio (< 9:10) and age | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and gender | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and insurance type | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and number of dispensings | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and dual drug therapy | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and Rx for depression | Chi-Square | Table 3b (3) |
| Change in dose and Age | Chi-Square | Table 4a (2) |
| Change in dose and Gender | Chi-Square | Table 4a (2) |
| Change in dose and Insurance Type | Chi-Square | Table 4a (2) |
| Change in dose and Number of Dispensings | Chi-Square | Table 4a (2) |
| Change in dose and Medication Possession Ratio | Chi-Square | Table 4a (2) |
| Change in drug and Age | Chi-Square | Table 4a (2) |
| Change in drug and Gender | Chi-Square | Table 4a (2) |
| Change in drug and Insurance Type | Chi-Square | Table 4a (2) |

| | | |
|---|---|---|
| Change in drug and Number of Dispensings | Chi-Square | Table 4a (2) |
| Change in drug and Medication Possession Ratio | Chi-Square | Table 4a (2) |
| Change in dose or drug and Age | Chi-Square | Table 4a (2) |
| Change in dose or drug Gender | Chi-Square | Table 4a (2) |
| Change in dose or drug Insurance Type | Chi-Square | Table 4a (2) |
| Change in dose or drug and Number of Dispensings | Chi-Square | Table 4a (2) |
| Change in dose or drug and Medication Possession Ratio | Chi-Square | Table 4a (2) |
| Medication possession and DV Dose change | PROC LOGISTIC | Table 5a (2) |
| Age and DV Dose change | PROC LOGISTIC | Table 5a (2) |
| Gender and DV Dose change | PROC LOGISTIC | Table 5a (2) |
| Number of dispensings and DV Dose change | PROC LOGISTIC | Table 5a (2) |
| Insurance type and DV Dose change | PROC LOGISTIC | Table 5a (2) |
| Medication possession and DV Change in drug dispensed | PROC LOGISTIC | Table 6a (2) |
| Age and DV Change in drug dispensed | PROC LOGISTIC | Table 6a (2) |
| Gender and DV Change in drug dispensed | PROC LOGISTIC | Table 6a (2) |
| Number of dispensings and DV Change in drug dispensed (DV) | PROC LOGISTIC | Table 6a (2) |

| | | | |
|---|---|---|---|
| | Insurance type and DV Change in drug dispensed | PROC LOGISTIC | Table 6a (2) |
| Patients receiving metformin only | Medication possession ratio (< 8:10) and age | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and gender | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and insurance type | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and number of dispensings | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and dual drug therapy | Chi-Square | Table3a (3) |
| | Medication possession ratio (< 8:10) and Rx for depression | Chi-Square | Table3a (3) |
| | Medication possession ratio (< 9:10) and age | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and gender | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and insurance type | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and number of dispensings | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and dual drug therapy | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and Rx for depression | Chi-Square | Table 3b (3) |
| | Change in dose and Age | Chi-Square | Table 4b (2) |
| | Change in dose and Gender | Chi-Square | Table 4b (2) |
| | Change in dose and Insurance Type | Chi-Square | Table 4b (2) |
| | Change in dose and Number of Dispensings | Chi-Square | Table 4b (2) |

| | | |
|---|---|---|
| Change in dose and Medication Possession Ratio | Chi-Square | Table 4b (2) |
| Change in drug and Age | Chi-Square | Table 4b (2) |
| Change in drug and Gender | Chi-Square | Table 4b (2) |
| Change in drug and Insurance Type | Chi-Square | Table 4b (2) |
| Change in drug and Number of Dispensings | Chi-Square | Table 4b (2) |
| Change in drug and Medication Possession Ratio | Chi-Square | Table 4b (2) |
| Change in dose or drug and Age | Chi-Square | Table 4b (2) |
| Change in dose or drug Gender | Chi-Square | Table 4b (2) |
| Change in dose or drug Insurance Type | Chi-Square | Table 4b (2) |
| Change in dose or drug and Number of Dispensings | Chi-Square | Table 4b (2) |
| Change in dose or drug and Medication Possession Ratio | Chi-Square | Table 4b (2) |
| Medication possession and DV Dose change (DV**) | PROC LOGISTIC | Table 5b (2) |
| Age and DV Dose change | PROC LOGISTIC | Table 5b (2) |
| Gender and DV Dose change | PROC LOGISTIC | Table 5b (2) |
| Number of dispensings and DV Dose change | PROC LOGISTIC | Table 5b (2) |
| Insurance type and DV Dose change | PROC LOGISTIC | Table 5b (2) |
| Medication possession and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |

| | | |
|---|---|---|
| Age and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Gender and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Number of dispensings and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Insurance type and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Medication possession and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Age and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Gender and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Number of dispensings and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |
| Insurance type and DV Change in drug dispensed | PROC LOGISTIC | Table 6b (2) |

| | | | |
|---|---|---|---|
| Patients receiving both sulfonylurea and metformin | Medication possession ratio (< 8:10) and age | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and gender | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and insurance type | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and number of dispensings | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and dual drug therapy | Chi-Square | Table3a (3) |
| | Medication possession ratio (< 8:10) and Rx for depression | Chi-Square | Table3a (3) |
| | Medication possession ratio (< 9:10) and age | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and gender | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and insurance type | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and number of dispensings | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and dual drug therapy | Chi-Square | Table 3b (3) |
| | Medication possession ratio (< 9:10) and Rx for depression | Chi-Square | Table 3b (3) |
| Patients receiving sulfonylurea only, metformin only, or both drugs | Medication possession ratio (< 8:10) and age | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and gender | Chi-Square | Table 3 (2) |
| | Medication possession ratio (< 8:10) and insurance type | Chi-Square | Table 3 (2) |

| | | |
|---|---|---|
| Medication possession ratio (< 8:10) and number of dispensings | Chi-Square | Table 3 (2) |
| Medication possession ratio (< 8:10) and dual drug therapy | Chi-Square | Table3a (3) |
| Medication possession ratio (< 8:10) and Rx for depression | Chi-Square | Table3a (3) |
| Medication possession ratio (< 9:10) and age | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and gender | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and insurance type | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and number of dispensings | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and dual drug therapy | Chi-Square | Table 3b (3) |
| Medication possession ratio (< 9:10) and Rx for depression | Chi-Square | Table 3b (3) |
| Mono versus dual therapy and DV Medication possession ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Age category and DV Medication possession ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Gender and DV Medication possession ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Number of dispensings and DV Medication possession ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Insurance type and DV Medication possession Ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Rx for anti-depressant and DV Medication possession ratio (< 8:10) | PROC LOGISTIC | Table 4a (3) |
| Mono versus dual therapy and DV Medication possession ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |

| | | |
|---|---|---|
| Age category and DV Medication possession ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |
| Gender and DV Medication possession ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |
| Number of dispensings and DV Medication possession ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |
| Insurance type and DV Medication possession Ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |
| Rx for anti-depressant and DV Medication possession ratio (< 9:10) | PROC LOGISTIC | Table 4b (3) |

**Table 4c. Summary of Multivariate Analyses Performed**

| Population | Description | Procedure | Table #; (manuscript #) |
|---|---|---|---|
| Patients receiving sulfonylurea only | Assessment of Colinearity between independent variables: DV = Dose change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Drug change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Dose or Drug change | PROC REG / COLLIN | n/a |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Dose change | PROC LOGISTIC | Table 7 (2) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Drug change | PROC LOGISTIC | Table 7 (2) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Dose or Drug change | PROC LOGISTIC | Table 7 (2) |
| | All independent variables and DV Dose change | PROC LOGISTIC | Table 8a (2) |
| | Ivs MPR and AGE category and DV Dose change | PROC LOGISTIC | Table 8a (2) |
| | All independent variables and DV Drug change | PROC LOGISTIC | Table 8b (2) |
| | IV AGE category and DV Drug change | PROC LOGISTIC | Table 8b (2) |

| | | |
|---|---|---|
| All independent variables and DV Drug or Dose change | PROC LOGISTIC | Table 8c (2) |
| IV AGE category and DV Drug or Dose change | PROC LOGISTIC | Table 8c (2) |

| | | | |
|---|---|---|---|
| Patients receiving metformin only | Assessment of Colinearity between independent variables: DV = Dose change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Drug change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Dose or Drug change | PROC REG / COLLIN | n/a |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Dose change | PROC LOGISTIC | Table 7 (2) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Drug change | PROC LOGISTIC | Table 7 (2) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Dose or Drug change | PROC LOGISTIC | Table 7 (2) |
| Patients receiving sulfonylurea only or metformin only | Assessment of Colinearity between independent variables: DV = Dose change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Drug change | PROC REG / COLLIN | n/a |
| | Assessment of Colinearity between independent variables: DV = Dose or Drug change | PROC REG / COLLIN | n/a |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Dose change | PROC LOGISTIC | Table 7 (2) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic): DV = Drug change | PROC LOGISTIC | Table 7 (2) |

| | | | |
|---|---|---|---|
| | Likelihood ratio test for interactions between independent variables (-2log statistic):<br>DV = Dose or Drug change | PROC LOGISTIC | Table 7 (2) |
| | All independent variables and DV Dose change | PROC LOGISTIC | Table 9a (2) |
| | All independent variables and DV Drug change | PROC LOGISTIC | Table 9b (2) |
| | All independent variables and DV Drug or Dose change | PROC LOGISTIC | Table 9c (2) |
| | All independent variables and DV Dose change | PROC LOGISTIC | Table 10a (2) |
| | Ivs MPR and AGE category and DV Dose change | PROC LOGISTIC | Table 10a (2) |
| | All independent variables and DV Drug change | PROC LOGISTIC | Table 10b (2) |
| | IV AGE category and DV Drug change | PROC LOGISTIC | Table 10b (2) |
| | All independent variables and DV Drug or Dose change | PROC LOGISTIC | Table 10c (2) |
| | Ivs MPR and AGE category and DV Drug or Dose change | PROC LOGISTIC | Table 10c (2) |
| All patients receiving sulfonylurea, metformin, or both | Likelihood ratio test for interactions between independent variables (-2log statistic):<br>DV = MPR < 8:10 | PROC REG / COLLIN | Table 5 (3) |
| | Likelihood ratio test for interactions between independent variables (-2log statistic):<br>DV = MPR < 9:10 | PROC REG / COLLIN | Table 5 (3) |
| | All independent variables and DV MPR < 8:10 | PROC LOGISTIC | Table 6a (3) |
| | All independent variables and DV MPR < 9:10 | PROC LOGISTIC | Table 6a (3) |

| | | |
|---|---|---|
| Ivs Mono versus dual therapy, Age category, and Number of dispensings and DV MPR < 8:10 | PROC LOGISTIC | Table 7a (3) |
| Ivs Mono versus dual therapy, Age category, and Number of dispensings and DV MPR < 9:10 | PROC LOGISTIC | Table 7b (3) |
| Ivs Mono versus dual therapy and Age category and DV MPR < 8:10 | PROC LOGISTIC | Table 8a (3) |
| Ivs Mono versus dual therapy and Age category DV MPR < 9:10 | PROC LOGISTIC | Table 8b (3) |

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## Appendix C. Overview of Major Findings

The objective of the analyses described in manuscript 1 was to assess hypoglycemic drug utilization; and specifically, to identify which hypoglycemic agents were most frequently utilized and what differences in utilization and direct costs may exist between age categories, genders, or insurance types.

Sulfonylureas were the most frequently prescribed class of hypoglycemic medication. Greater than half of all patients (56.8%) and greater than three-quarters of patients receiving oral therapy (75.7%) received a dispensing for a sulfonylurea. Metformin was the next most frequently prescribed oral agent: 20.9% of all patients and 27.6% of patients receiving oral therapy received at least one dispensing for metformin. Troglitazone was the third most frequently utilized oral medication. During the 12-month period, 16.04% of all patients received a dispensing for troglitazone. The use of this agent was most frequent among younger diabetics: 20.3% of patients age 40 – 49 years received a dispensing for troglitazone; only 10.2% of seniors received a dispensing for this agent. Of the other newer hypoglycemic medications, glimepramide, repaglinide, and acarbose were each dispensed to less than 5% of all patients.

During the 12-month period, patients frequently experienced a change in hypoglycemic medication(s) dispensed. The most frequently observed change

in drug regimen was for patients dispensed sulfonylurea only. The percentage of patients categorized as receiving only a sulfonylurea decreased by 8.76%, the largest percent change for any drug regimen category. Changes in drug regimen utilized were also frequent. Of patients categorized as receiving only a sulfonylurea during the first 90 days of the 12-month period, 74% remained using the same regimen during the last 90 days of the 12-month period. For patients initially categorized as receiving both a sulfonylurea and metformin, 70% were similarly classified based upon dispensings during the last there months. Thus, 26% and 30% of patients receiving sulfonylurea or sulfonylurea plus metformin respectively changed regimen during the 12-month period. Similar magnitude changes were observed for the other less frequently utilized regimens, and ranged from a low of 18% for patients receiving insulin only to a high of 70% among patients receiving insulin plus an oral agent other than troglitazone. Based on these results, it was concluded that the diabetic patients in this population frequently changed medication regimen, possibly as a result of worsening glucose control, inconsistent refill patterns (nonadherence), or desire to utilize new therapies.

Patients 65 years of age or older were less frequently dispensed troglitazone or metformin as monotherapy, and more frequently received dispensings for sulfonylureas. The less frequent use of troglitazone and metformin in older patients may reflect an increased prevalence of contraindicating co-morbidities. Increased duration of disease may be a potential explanation for

the greater utilization of sulfonylureas in older patients. Such patients may have been more likely to have initiated treatment in earlier years, when sulfonylureas were the primary oral therapeutic option.

Differences in the 12-month cost of hypoglycemic medication utilized reflect the differing patterns of drug use among age groups. Drug utilization costs were lowest among older patients, who more frequently received dispensings for lesser-cost sulfonylurea products. The total 12-month cost of medication dispensed was not significantly different among patients under 50 years of age and between 50 and 64 years of age.

The analyses described in manuscript 2 provided insight into the relationship between adherence to therapy and changes in the drug regimen. It was hypothesized poor glucose control would result from failure to possess a sufficient quantity of medication necessary to be adherent. The proxy for poor glucose control used in these analyses was a change in dose of hypoglycemic medication dispensed or a change in the class of hypoglycemic drug dispensed.

A change in dose of sulfonylurea or metformin was more than twice as frequently observed than a change in type of hypoglycemic medication dispensed for both users of sulfonylureas (change in dose: 58.53%, change in drug 26.78%) and metformin (change in dose: 48.19%, change in drug

18.07%). Among all patients dispensed either a sulfonylurea or metformin only, 57% received medication at different dosages during the 12-month period; 58.5% of patients receiving a sulfonylurea and 48.2% of patients receiving metformin did not receive the same dose of medication throughout the 12-month period.

In both bivariate and multivariate analyses of patients receiving dispensings for sulfonylurea only, possession of medication for less than 8 of 10 days was associated with an increased likelihood of a change in dose of medication dispensed in subsequent months. A similar effect was observed among patients in the combined sample of patients receiving a sulfonylurea or metformin. Based upon the results of multivariate analyses, such patients were 36% more likely to receive a dispensing for a different strength of drug (OR 1.36, 95% CI 1.02 – 1.83). A statistically significant association between possession of metformin and change in dose dispensed was not observed, possibly due to a lack of power to detect such an effect based on the lesser number of such patients.

Among users of sulfonylureas, medication possession was associated with the combined outcome of change in medication dose or change in type of hypoglycemic medication dispensed. This association was also observed in analyses based upon the combined sample of patients receiving dispensings for sulfonylurea or metformin only. Such an association was not observed

among patients receiving dispensings for metformin only. Additionally, medication possession was not found to be associated with the sole outcome of change of type of hypoglycemic medication dispensed for the sulfonylurea only, metformin only, and combined samples.

Age was associated with medication possession. Patients under 50 years of age were most frequently categorized as not possessing a quantity of medication sufficient to cover eight of ten days in the assessment period. This difference was only statistically significant for users of sulfonylurea monotherapy. This sample included nearly six times as many patients as the metformin sample (sulfonylurea: n = 967; metformin: n = 166). Age was also found to be significant in multivariate analyses assessing the association between medication possession and change in regimen utilized or dose dispensed. As compared with younger patients, sulfonylurea users 65 years of age or older were 43% less likely to receive a different dose of hypoglycemic medication during the 12-month period (OR 0.57, 95% CI 0.40 - 0.81). Such patients were also 48.5% less likely to receive a medication other than a sulfonylurea during the 12 months (OR 0.52, 95% CI 0.34 - 0.78). These relationships were not found to be significant for analyses based upon the smaller sample of patients who received dispensings for metformin only.

Among patients dispensed either sulfonylureas or metformin, those dispensed a greater number of prescriptions for any health condition were less frequently

categorized as failing to possess medication for less than 80% of days. The outcomes of change in dose or change in class of medication dispensed were not found to be significantly influenced by differences in the medication possession ratio.

The aims of the analyses described in manuscript 3 were to assess adherence with hypoglycemic medication via the medication possession ratio and to compare medication possession among patients dispensed either monotherapy with sulfonylurea or metformin with patients receiving dual therapy with both medications. Additionally, we examined the association between medication possession and age, gender, insurance plan, the total number of dispensings, and the dispensing of a medication typically used to treat depression.

Based upon medication possession, adherence to any hypoglycemic drug regimen was frequently sub-optimal. Greater than one in four of all patients studied (28.8%) did not receive a quantity of medication sufficient to cover 8 of 10 days in the period. Only 59.5% of all patients possessed medication at a ratio equal to or exceeding 9:10. Medication possession was highest among patients who received dispensings for sulfonylureas only (MPR >= 8:10: 77.2%, MPR >= 9:10: 66.8%). Patients receiving dispensings for metformin only were less adherent, with 71.1% and 56.6% of patients possessing medication for at least eight of ten or nine of ten days in the assessment

period, respectively. The least adherent sub-population was patients receiving dispensings for both metformin and sulfonylureas. Less than half of such patients possessed medication for at least nine of ten days (43.1%), while 56.9% of patients received at least enough medication to cover eight of ten days.

In both bivariate and multivariate logistic models, dual therapy with a sulfonylurea and metformin was associated with an increased likelihood of failure to possess medication for at least eight of ten and nine of ten days. In bivariate logistic analyses, patients were nearly 2.5 times more likely to be classified as nonadherent if they received dispensings for both drugs (MPR < 8:10: OR 2.44, 95% CI 1.92 – 3.10; MPR < 9:10: OR 2.49, 95% CI 1.97 – 3.14). Multivariate analyses controlling for the influence of age and the total number of dispensings were also conducted. Based upon these analyses, and as compared with a one drug regimen, the use of dual therapy was associated with a greater than three-fold increase in the likelihood of being classified as nonadherent for both the 8:10 and 9:10 MPR thresholds (MPR < 8:10: OR 3.14, 95% CI 2.42 – 4.08; MPR < 9:10: OR 3.20, 95% CI 2.49 – 4.118).

Of the five potential confounding variables examined, only age and the total number of dispensings were significant influences on medication possession. Based upon bivariate logistic regression analyses, patents 65 years of age or

older were 52.1% less likely to be classified as nonadherent as compared with patients of younger age, using an MPR threshold of less than 8:10 (OR 0.48, 95% CI 0.35 - 0.65). Seniors were 42.4 % less likely to be classified as nonadherent based upon the MPR threshold of less than 9:10 (OR 0.58, 95% CI 0.44 - 0.76). Patients receiving 12 or more dispensings for any type of medication were 44.6% less likely to be classified as nonadherent based upon the 8:10 MPR threshold (OR 0.56, 95% CI 0.35 - 0.65), and 42.3% less likely based upon the 9:10 MPR threshold (OR 0.57, 95% CI 0.47 - 0.70). Three other potential confounding variables were examined: gender, insurance type and receiving a dispensing for an antidepressant. None of these variables were found to be a significant influence on medication possession.

In sum, the hypoglycemic drug utilization patterns of diabetic patients and various sub-populations can be characterized as frequently changing, and differing substantially between age categories. Older patients in this population more frequently received dispensings for sulfonylureas only, less frequently received dispensings for troglitazone or metformin as monotherapy, and more likely to refill prescriptions when due. Additionally, the 12-month total cost of all hypoglycemic medication dispensed was lowest among patients 65 years of age and older. Gender and insurance type were not found to be significantly associated with medication possession, or with change in medication dose or type of medication dispensed. Medication possession was found to be associated with an increase in the likelihood of

receiving a dispensing for a different strength of hypoglycemic medication among sulfonylurea users, and among a combined sample of patients receiving dispensings for with sulfonylurea or metformin only. Medication possession was often sub-optimal for what would be deemed sufficient for achieving tight glucose control. Patients were found to be least likely to possess medication when both a sulfonylurea and metformin were used as dual therapy, as compared with patients receiving either agent as monotherapy.

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