

Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population

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OBJECTIVE — Clinical trials provide information regarding the safety and efficacy of medications used to manage type 2 diabetes but do not elucidate drug effectiveness in a typical managed care environment. The aim of this study was to characterize “real-world” drug utilization patterns from both a prescriber and a patient perspective.

RESEARCH DESIGN AND METHODS — We conducted a retrospective analysis of a large administrative pharmacy claims database, using data on continuously pharmacy benefit-eligible members prescribed oral hypoglycemic agents (OHAs).

RESULTS — The 12-month persistence rate for the OHA cohort was low, ranging from 31% for α -glucosidase inhibitors to 60% for metformin; compliance rates varied between 70 and 80%. During the first 12 months of therapy, 36% of the patients remaining on therapy at 12 months had one or more therapy modifications. The mean number of therapy changes increased with the length of patient follow-up, with more than half of all patients experiencing at least one therapy change over the duration of follow-up.

CONCLUSIONS — These findings document the wide variation in utilization patterns associated with pharmacological management of type 2 diabetes, suggesting that opportunity exists to optimize its pharmacological management.

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D iabetes is a prevalent multisystem metabolic disease associated with high health care resource expenditures. The American Diabetes Association (ADA) estimated that in 1997, ~10.2 million (5.1%) U.S. adults were newly diagnosed with diabetes, with another 5.4 million people (2.7%) unaware that they had the disease (1). Of the U.S. population aged 40–74 years, the prevalence of diabetes increased from 8.9% during 1976–1980 to 12.3% during 1988–1994 (2). The costs of managing diabetes and its complications comprise ~15% of total

U.S. health care expenditures (3). In 1997, direct medical health care expenditures for diabetes care were estimated to exceed \$44.1 billion, with the majority of these costs related to inpatient care (62%), followed by outpatient services (25%) and nursing home care (13%) (4).

The benefits of lowering or normalizing blood glucose levels in the management of type 2 diabetes was conclusively demonstrated in the U.K. Prospective Diabetes Study (UKPDS) (5). Whereas randomized controlled clinical trials traditionally provide useful information

on drug safety and efficacy, drug-utilization patterns and clinical effectiveness in a “real-world” setting may differ substantially from the data provided from such trials. In particular, agent tolerability, drug-drug interactions, and the use of complicated drug regimens may lead to poor compliance or discontinuation with prescribed medications, resulting in reduced clinical effectiveness. Data from the Third National Health and Nutrition Examination Survey found that many U.S. adults with type 2 diabetes have unacceptable levels of glycemic control. Furthermore, only 37.7% of the patients treated with oral hypoglycemic agents (OHAs) were found to have HbA_{1c} values <7%, a level the ADA considers the goal for patients with diabetes (6). Fasting plasma glucose and HbA_{1c} levels have been noted to drift upwards subsequent to long-term treatment with sulfonylureas, metformin, or diet and exercise (5). Similar results were observed in another claims database analysis, where regimen complexity and low self-reported compliance were also seen for sulfonylurea therapy (7). This lack of glycemic control places diabetic patients at high risk for accelerated disease progression and its sequelae.

Most often, clinical effectiveness is influenced by prescriber agent selection and therapy changes as well as patient adherence with prescribed drug regimens. Drug utilization studies using administrative pharmacy claims data can provide useful insights into the prescribing patterns and patient medication-taking behavior in typical usual-care settings (8,9). The purpose of this study was to evaluate the drug utilization parameters associated with pharmacological management of type 2 diabetes among members of a large drug-insured population.

RESEARCH DESIGN AND METHODS

New OHA therapy cohort construction

Administrative pharmacy claims for >60 million Americans from the Merck-Medco Managed Care (MMMC) informa-

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Abbreviations: ADA, American Diabetes Association; AGI, α -glucosidase inhibitor; OHA, oral hypoglycemic agent; MMMC, Merck-Medco Managed Care; SDDS, same drug and same dose; UKPDS, U.K. Prospective Diabetes Study.

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

tion warehouse were used to support this analysis. The MMMC information warehouse is a database containing 3 years of longitudinal patient-level pharmacy claims data. The cohort was reflective of the payer mix in the U.S. health care market, with membership including drug-insured individuals from health care insurance carriers, managed care organizations, employers, retirement organizations, and other payer sources.

Members affiliated with clients whose records were available for research purposes ($n = \sim 46$ million) were identified for cohort construction. Subjects continuously benefit-eligible for mail and retail prescriptions from 1 April 1997 through 31 May 2000 were queried for preliminary inclusion ($n = 11.6$ million). From this population, a new-start cohort was identified, consisting of patients receiving a first prescription for OHA therapy between 1 October 1997 and 31 March 1999. Patients without OHA or insulin use during the 6 months preceding the first prescription during the identification window (the "index prescription") were included in the final cohort ($n = 136,466$). Patients using insulin during the identification period were excluded. All utilization analyses were performed relative to the index agent and were inclusive of a study period from 1 October 1997 to 31 May 2000, supporting individual patient follow-up of 14–32 months.

Members with mail service prescriptions for OHAs were excluded because these prescriptions generally contain a greater drug supply and may reflect different drug-taking behavior than retail service. This study was therefore restricted to patients who received 100% of their OHA prescriptions via retail channels ($n = 85,883$). Patients were further classified as initial OHA monotherapy or initial combination therapy. The latter was defined as patients who started a second OHA within 7 days of their index prescription ($n = 6,385$). For study purposes, a new-start retail-only OHA cohort, consisting of patients initiating OHA monotherapy between 1 October 1997 and 31 March 1999, was used for analytical purposes ($n = 79,498$). Pioglitazone and rosiglitazone patients were excluded from the analysis of the glitazone class because those agents became available after the study identification period and thus

Table 1—Utilization rates of OHAs during the first 12 months of therapy

	Metformin	Sulfonylureas	Troglitazone	AGI	Repaglinide	Total
<i>n</i>	19,295	52,813	5,273	885	1,232	79,498
Compliance (mean)	76.4	80.1	83.0	70.4	69.8	79.2
Add concomitant agent	18.6	13.0	18.0	16.2	12.7	14.7
Discontinuation	11.9	11.3	8.3	10.2	16.2	11.3
Increase dose	30.7	23.6	21.4	14.9	28.6	25.2
Decrease dose	11.7	10.7	8.0	9.5	17.7	10.9
Switch	8.9	10.4	13.8	16.2	9.5	10.3
Secondary failure	21.8	19.1	24.7	23.1	17.1	20.1

Data are %.

had inadequate (≤ 12 months) follow-up data to support this analysis.

Study definitions

Patient age was calculated as of the date of the index prescription fill. Duration of prescribed therapy was defined as the number of days between a patient's first and last prescription fill dates within the study time frame. Because patients in the final cohort had different lengths of follow-up, defined as time between the initial OHA prescription and the end of the study period, all analyses were stratified by length of follow-up (14–18, 18–23, and > 24 months). In addition, utilization parameters were assessed for the entire cohort for the 12 months following the index study prescription.

The drug utilization parameters evaluated included compliance, persistence, discontinuation, concomitance, switching, and titration. Compliance and persistence for OHAs were calculated based on "days' supply," defined as the number of days the dispensed drug supply should last based on prescriber dosing instructions and the number of pills dispensed. Compliance was measured as the sum of the days' supply of a patient's prescriptions dispensed from the index prescription date to the last fill date (excluding the days' supply dispensed at the last fill) divided by the patient's duration of therapy. Compliance was calculated for subjects with at least two fills of the index OHA. Persistence (yes/no) was based on patient refill behavior to support at least 1 day's supply of the index OHA at any time during the n th month post-index date with a 30-day window. Discontinuation was characterized as patients ending therapy on the index OHA and not receiving a fill within x days of supply exhaustion of an OHA prescription, where x equals 150% of the days' supply of the last fill.

Concomitance, or addition of another OHA, was defined as starting a nonindex medication while obtaining a refill for the index drug within a specified window (index drug fill date + $2.5 \times$ [days' supply of index drug fill]). Agent switching among OHAs was defined as starting a different drug 30 days after the date of index fill while not obtaining a refill for the index drug within $2.5 \times$ [days' supply of the previous index drug fill] from the index fill date. Upward and downward titration rates were calculated for all agents of interest, using thresholds based on dosage changes between two successive fills that were clinically relevant, defined as any valid combination of medication strengths consistent with dosing approved for that agent (10). Definitions for utilization parameters used in the present study are similar to those found in the published literature for similar database studies (9,11).

The same drug and same dose (SDSD) metric represented patients who did not discontinue therapy, switch from the initial agent, add concomitant therapy in the first 12 months of therapy, or have a gap of > 15 days between fills. This analysis was performed for selected agents. Secondary failure was defined as a patient adding one or more concomitant OHAs and/or switching from the initial OHA to a different agent (12,13). Finally, therapy change was defined as a combined utilization metric that included therapy augmentation, dosage adjustments (up or down), or switching to another OHA.

RESULTS — The new-start, retail-only OHA cohort ($n = 85,888$) consisted primarily (92.6%) of monotherapy patients ($n = 79,498$). The mean age of the cohort (mean \pm SD) was 60.1 ± 14 , and 0.4, 61.9, and 37.7% of these patients were in the < 18 , 18–64, and ≥ 65 years of age

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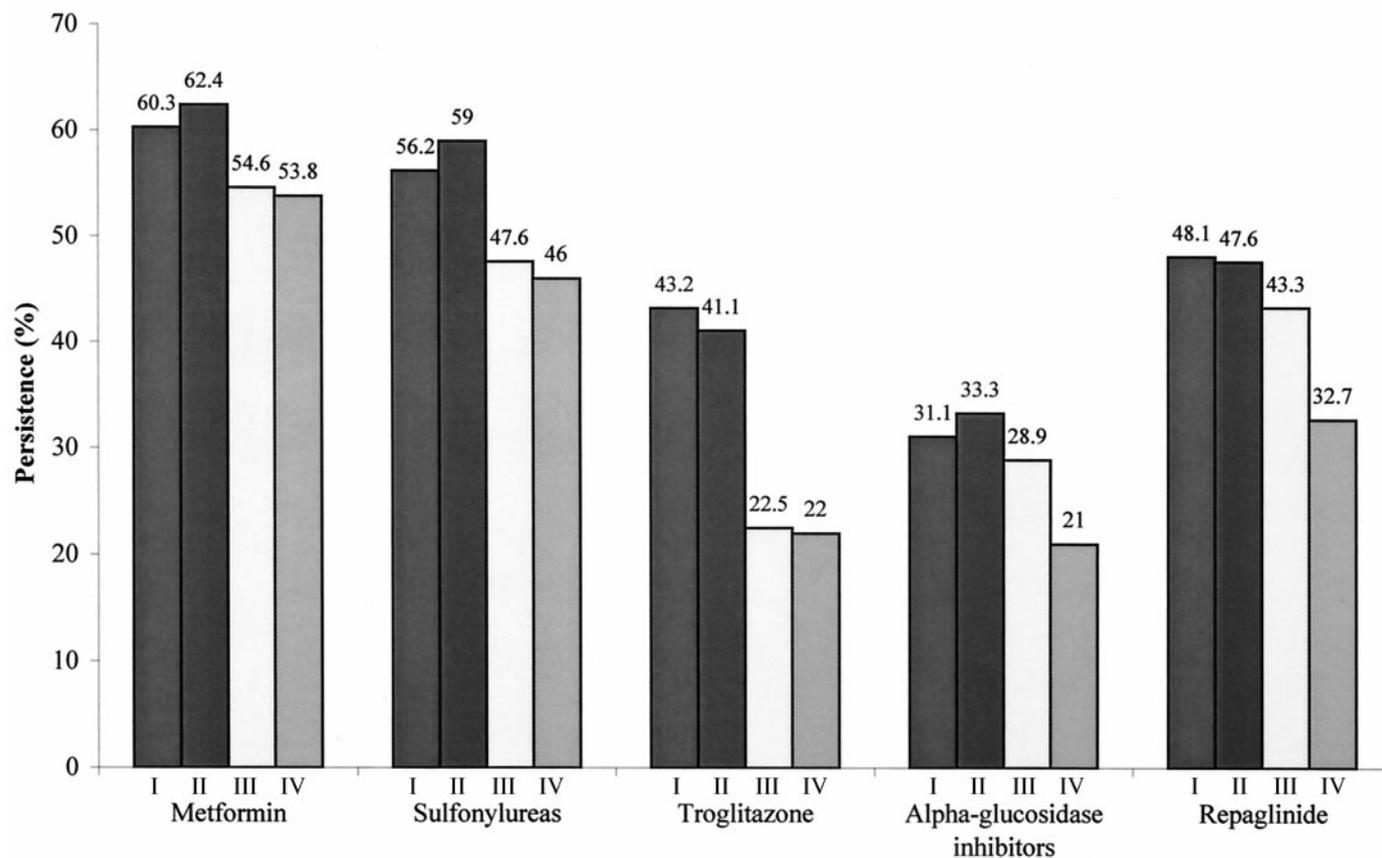


Figure 1—Persistence by month. Columns represent the *n*th month of persistence for each treatment. I, 12-month persistence (All); II, 12-month persistence (14- to 17-month follow-up); 18-month persistence, (18- to 23-month follow-up); 24th (24-month follow-up).

strata, respectively. The majority of the cohort (53.6%) was male. The distribution of initial OHA therapy was as follows: 66.4% sulfonylureas, 24.3% metformin, 6.6% troglitazone, 1.5% repaglinide, and 1.1% α -glucosidase inhibitors (AGIs).

The average 12-month patient compliance rate for all OHAs was \sim 79% (Table 1). In general, patient compliance decreased as the length of therapy increased. Similarly, the greatest compliance was observed with troglitazone therapy regardless of the length of follow-up, with the poorest mean compliance associated with both repaglinide therapy and AGIs at all lengths of follow-up. Persistence at 12 months was highest among metformin patients (60.3%) and lowest among AGI users (31.1%) (Fig. 1). Metformin patients were also the most persistent at all follow-up intervals compared with other OHA classes.

The rate of initial therapy discontinuation for all agents at 12 months was 11.3% (Table 1), with a mean time to discontinuation of 83 ± 71 days. Discontin-

uation rates generally increased with increasing length of OHA usage independent of agent (11.8, 17.0, and 19.2% for, respectively, <18 , 18–23, and 24+ months). Concomitant OHA therapy was initiated in 14.7% of patients within 12 months of their initial agent (Table 1). The average time to addition of a subsequent agent was 129 ± 108 days. Patients initiating therapy on metformin or troglitazone added concomitant OHAs most frequently (18.6 and 18.0%, respectively) (Table 1).

We found that \sim 10% of patients switched to a different agent within 12 months of OHA therapy initiation. Patients initiating an AGI most frequently switched to another OHA, and the time to first switch was longest for metformin (220 ± 135 days) and sulfonylureas (186 ± 130 days). Switch rates remained consistent for all agents regardless of follow-up duration. We also found that \sim 20% of patients initiated on OHA experienced secondary failure at 12 months. Secondary failure for all agents also in-

creased with increasing therapy duration. Dosage increases were fairly common, with 25.2% of patients having one or more dosage increases within 12 months of the index OHA. Dose titrations in metformin (30.7%) and repaglinide (28.6%) patients occurred more frequently than in patients receiving other agents. These dosage increases were more commonly observed with increasing lengths of follow-up (28.2, 32.7, and 37.4% with <18 , 18–23, and ≥ 24 months follow-up, respectively). We found that \sim 11% of the cohort decreased initial OHA dosage within 12 months. This trend also increased with duration of follow-up (13.0, 15.3, and 19.7% at <18 , 18–23, and ≥ 24 months, respectively). Repaglinide patients decreased dosage more frequently at 12 months than other OHA patients (17.7%) (Table 1).

Among patients initiating any OHA, 34.6% remained on the SDS for 12 months, with ≤ 15 days between refills. Patients initiating therapy on troglitazone had the highest percentage remaining on

Table 2—Oral hypoglycemic therapy changes during first 12 months of therapy

	Metformin (n)	Sulfonylureas (n)	Troglitazone (n)	AGI (n)	Repaglinide (n)	Total* (n)
First 12 months of OHA therapy	6,501	16,422	1,088	257	222	25,202
Mean number of therapy changes	2	2	2	2	2	2
Percentage of patients with ≥ 2 changes	50.6	45.9	43.2	47.9	39.6	46.9
Percentage of patients with ≥ 3 changes	22.9	20.7	17.7	16.3	12.6	20.9

Data limited to patients with therapy changes (switching, adding, or titration). *Excludes patients who discontinued therapy.

the SDSA (40.5%) for 12 months of therapy, whereas those on glimiperide retained the lowest percentage (28.4%) on the SDSA for 12 months. To further explore the continuation of the initial OHA prescribed, the total number of therapy changes during the first 12 months was evaluated for the entire cohort (Table 2). We found that 36% of the patients who did not discontinue therapy during the first 12 months had one or more therapy change, with a mean time to first change of 108 ± 99 days. Patients with therapy changes averaged two therapy modifications during the first 12 months of study follow-up regardless of initial agent (Table 2). The proportion of the cohort remaining on therapy with one or more therapy changes was higher for those with ≥ 24 months of follow-up (47.7, 46.7, and 54.0% for <18 , 18–23, and ≥ 24 months, respectively). These findings were consistent across all OHAs.

CONCLUSIONS — The focus of this study was to evaluate physician prescribing and patient utilization patterns associated with oral pharmacological management of diabetes in patients with prescription benefit coverage. Unlike clinical trials that typically address issues related to safety and efficacy, this study attempted to provide data on real world effectiveness by characterizing utilization behavior associated with OHAs. Unfortunately, this data source could not support an evaluation of glycemic control associated with OHA utilization, but rather focused on characterizing prescriber behavior and patient adherence related to these classes of agents.

These data clearly confirm the disparity associated with pharmacological management of chronic diseases, as evidenced by the differences in patient compliance and persistence as well as prescriber factors related to agent selection and changes in therapy. The 12-month OHA monotherapy persistence was low, ranging

from 31% for AGI to 60% for metformin, with compliance rates of 70–83%. These rates were similar to those observed in another study of oral hyperglycemic patients (14). Additionally, compliance rates steadily declined with increasing duration of therapy in this study. Given the chronic debilitating aspects of this disease, the importance of patient adherence is essential for the glycemic control necessary to avoid the micro- and macrovascular complications of diabetes.

In this study, therapy discontinuation rates were between 8 and 16%, consistent with data from a similar study showing that 8–10% of sulfonylurea and insulin users discontinued their medication over the study period (12). In addition, upward dosage changes were observed in 15–31% of the current study cohort. As would be expected, this need for dosage titration was associated with increasing duration of therapy, reinforcing issues related to agent efficacy or progression of the disease process as manifested by changes in insulin resistance, sensitivity, or production. The addition of a second agent was observed in 15% of the population, with a mean time to therapy augmentation of ~ 4 months; switching to another OHA occurred infrequently ($\sim 10\%$).

When a composite utilization end point of any therapy change was evaluated at 12 months post-OHA initiation, a striking 36% required some form of therapy change to manage their disease. Another study by Wetzler and Snyder (13) described suboptimal control of type 2 diabetes with a monotherapeutic approach, showing that 27% of patients remained on the same monotherapy agent, even though they failed to achieve an HbA_{1c} level $< 8\%$. Another important aspect of this study was the evaluation of the mechanism and time to OHA therapy failure. Primary failure of OHA, defined as the inability to achieve metabolic control when OHAs are first initiated (15), could

not be included in this study because a measure of glycemic control was not available. However, in the UKPDS trial, patients whose HbA_{1c} levels were lowered with the use of sulfonylureas showed a subsequent upward HbA_{1c} drift with continued therapy (5). The failure of OHAs to control blood glucose after a period of success is referred to as secondary failure (16). Because measures of glycemic control were not available in this study, a utilization proxy measure of switching or the addition of another agent was used to estimate secondary failure. Using this method, 20% of the cohort experienced secondary failure within the first 12 months of therapy.

Because this study was a retrospective analysis of OHA utilization patterns using pharmacy administrative claims from a large pharmacy benefit manager, it is important to recognize some inherent study limitations. This analysis reflected the utilization behavior of patients with a pharmacy benefit and thus could not include those who lack some form of insurance for pharmacy services. Consequently, compliance and persistency rates may have been higher than what would have been observed with patients paying cash for their medications. This study also excluded undiagnosed diabetic individuals and diagnosed diabetic patients who do not receive pharmacological therapy. Additionally, because of the data source used in this study, it was not possible to link these utilization data to measures of glycemic control or to information regarding disease severity. This study used drug markers (OHA or insulin) to characterize type 1 and type 2 diabetes, without diagnostic data to confirm the presence of diabetes. Despite the size and geographic diversity of the MMMC information warehouse ($n = 60+$ million covered individuals throughout the U.S.), the results may also not reflect the behavior of physicians and patients in the U.S. at large. In addition, issues related to co-pay amounts and

formulary management may contribute to variability in drug utilization. Despite these limitations, these factors are reflective of a real world managed care setting challenged with improving the delivery of quality health care while controlling escalating health care costs.

Achievement of HbA_{1c} levels below the ADA threshold for recommending action in managing diabetes (HbA_{1c} values <8%) will remain a challenge, given the variability in patient drug-taking behavior and physician prescribing. Despite these more intensive treatment guidelines, physicians will remain challenged to adequately manage type 2 diabetic patients with OHAs and to consider the treatment complexities associated with insulin therapy. It is clear that oral pharmacological therapy will remain an integral component in the armamentarium for management of diabetes. This study has demonstrated that the existing oral agents are associated with real world variability that is associated with physician prescribing as well as patient adherence, suggesting that opportunity exists to optimize diabetes pharmacological management. Future management of patients with diabetes should involve not only more efficient use of existing agents but hopefully future agents that will provide enhanced efficacy, tolerability, and real-world clinical effectiveness.

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