Persistence Patterns with Oral Hypoglycemic Agents in Type 2 Diabetes

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• Objectives: To determine persistence with therapy in patients newly starting oral hypoglycemic treatment for management of type 2 diabetes, and to determine differences in persistence according to sex, age, and initial agent.
• Design: Retrospective medication claims analysis.
• Setting and participants: 46,884 patients from a large U.S. pharmacy benefits manager (PBM) database who were older than 18 years of age and who newly started monotherapy with an oral agent for type 2 diabetes.
• Methods: All patients were followed for 10 months for refill persistence patterns with their initial drug. Agents included in the analysis were glimepiride, immediate-release glipizide, glipizide GITS (gastrointestinal therapeutic system), glyburide, metformin, pioglitazone, repaglinide, and rosiglitazone.
• Results: The overall average length of therapy was 167 days out of 300 days of follow-up. Women were significantly less persistent than men (161 days versus 173 days, respectively). Persistence significantly increased with patient age, from a low of 126 days (18–34 years) to 179 days (50–64 years), but then fell to 161 days (≥ 65 years). Significant differences were also identified for the oral agents, with persistence ranging from 126 days with repaglinide to 177 days with glipizide GITS.
• Conclusions: Overall persistence with the initial oral hypoglycemic drug treatment appears to be low in type 2 diabetes and differs within sex, age, and individual drug categories. Careful selection of the initial oral agent to minimize adverse events and reduce dosing frequency may improve persistence, enhance glycemic control, and reduce the economic burden of type 2 diabetes.

Diabetes is a costly and increasingly common chronic disease affecting more than 17 million persons in the United States; an estimated 5.9 million of these cases are undiagnosed [1]. Type 2 diabetes accounts for approximately 90% to 95% of all diagnosed diabetes cases and affects more than 20% of the population older than age 65 years [1]. The overall economic burden of diabetes in the United States is more than $100 billion annually [2]. Long-term glycemic control, achieved via a combination of lifestyle changes and the use of oral antidiabetic agents and insulin, has been found to significantly reduce morbidity and mortality [3,4]. Furthermore, effective management of diabetes to achieve glycemic control improves patient quality of life and is cost-effective [5,6].

Although the clinical and economic value of long-term glycemic control is clear and should be a priority, adherence to physician-prescribed oral therapy remains a challenge for patients with type 2 diabetes. Depending on the patient population, definitions, and methodology used, reported rates of adherence, compliance, or persistence with oral hypoglycemic treatment range from 16% to 79% [7–14].

Limited information exists on how treatment persistence differs across sex and age groups. For treatment with sulfonylureas, Sclar and colleagues found that men and younger patients were less persistent with their treatment than were women and older patients [7]. It is unclear whether these findings hold true for different patient populations. Furthermore, although several different effective oral hypoglycemic treatments are currently used in the United States, very little is known regarding persistence rates with these agents. Persistence may vary between agents that have different efficacy, side effect, and dosing profiles.

Clinicians seeking to tailor the antidiabetic drug regimen to the needs of their patients might benefit from increased knowledge on how persistence with these agents varies by patient demographics and class of agents. The objectives of this study were to determine the persistence with oral hypoglycemic agents in patients newly starting pharmacologic
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treatment for type 2 diabetes, and whether differences in persistence exist across patient sex and age groups and individual drug therapies.

Methods
Design
A retrospective database analysis was conducted using patient-specific drug refill information from a large national pharmacy benefits manager (PBM) in the United States, which processes over 300 million prescription claims annually. This prescription claims database contains the most recent 25 months of data covering the prescription claims of 50 million Americans in health plans throughout the country.

Patient Selection
To be included in the study, a patient (1) had to be 18 years of age or older; (2) had to have been continuously enrolled in the prescription claims database, implying that the patient had continuous drug insurance coverage; (3) had to have filled a prescription for an oral hypoglycemic agent (defined as any agent that reduces blood glucose levels) during a 4-month index period spanning from 1 September 1999 to 31 December 1999; and (4) must not have filled a prescription for an oral hypoglycemic agent during a 6-month preperiod from 1 March 1999 to 31 August 1999. Using these criteria, all patients included in the analysis were likely to be drug naive and newly diagnosed with type 2 diabetes. All patients were followed for 10 months after the initial prescription identified in the index period. Hence, the postperiod lasted through 31 October 2000. All patients included in the analysis had continuous drug insurance coverage starting from the 6-month preperiod through the entire analysis timeframe.

Patients were categorized and analyzed according to sex and age (18–34 years, 35–49 years, 50–64 years, and ≥ 65 years) and the oral hypoglycemic prescriptions they filled during the index period. These hypoglycemic drugs were immediate-release glipizide (brand and generic), glipizide GITS (gastrointestinal therapeutic system; Glucotrol XL), glimepiride (Amaryl), glyburide (brand and generic), metformin (Glucophage), pioglitazone (Actos), repaglinide (Prandin), and rosiglitazone (Avandia). We reviewed proprietary U.S. market research information (IMS data) to identify oral hypoglycemic agents with a market share greater than 1%. Because miglitol and acarbose (alpha-glucosidase inhibitors) had less than 1% market share during this period, they were not considered in the analysis.

Persistence was defined in terms of the number of days of uninterrupted treatment during the study’s follow-up period (ie, treatment with no more than a 30-day break in therapy). Patients received prescriptions for a standard 30-day supply of medication per refill, and persistence was calculated based on the number of days supplied. Among patients who interrupt ed their treatment for more than 30 days, we determined whether they resumed therapy with another oral agent within 60 days after discontinuation of their initial drug. This behavior was defined as a switch in drug treatment, and we evaluated the switching patterns within drug category. Evaluation/tracking of add-on therapies (ie, combination and triple therapies) was beyond the scope of our primary objective (ie, persistence with the initial oral hypoglycemic agent). Thus, patients defined as persistent in our study may have been receiving more that one oral hypoglycemic agent (over time, a second agent may have been added to the initial drug therapy).

Analysis
ANOVA testing was performed to compare differences in average length of therapy between all of the agents. We also conducted ANOVA for overall differences across age categories and sex categories within treatment groups. When the omnibus F-test for the ANOVA was significant, an appropriate post hoc analysis was conducted within each of the sex and age categories. Each of the drugs was contrasted with the average treatment duration of all drugs en mass within the sex or age category using a t test (one-tailed test for above and below the mean) with Bonferroni correction for multiple comparisons. This is a slightly more conservative post hoc contrast (meaning that differences had to meet a higher threshold before they were considered to be statistically significant). These 8 contrasts were viewed as more informative than all 28 pairwise sets of contrasts within each of the sex and age categories. The goal was to identify which treatment categories outperformed the whole group within each of the sex and age categories. Differences were considered statistically significant at the P = 0.05 level. Testing was performed using SAS (version 6.11, SAS Institute, Cary, NC).

Results
A total of 46,884 patients met the criteria for inclusion in the analysis and were available for analysis. Their demographic characteristics and distribution across drug categories are detailed in Table 1. Both sexes were evenly represented in the sample. Seventy-eight percent of the patients were older than 50 years of age and 41% were older than 65 years. The study demographics were generally consistent with other major studies of demographics in type 2 diabetes (eg, the National Health Interview Survey found that 45% of patients with newly diagnosed type 2 diabetes are men and 43% are aged 65 years or older) [15].

More than one third of patients initially filled prescriptions for metformin, 21% for glyburide, 15% for glipizide GITS, 10% for glimepiride, and between 3% to 10% for each of the other agents. While the distribution of patients across the drug groups was almost evenly split between the sexes, women received metformin and rosiglitazone more frequently than...
men (54% versus 46% for metformin, and 53% versus 48% for rosiglitazone). Some differences in initial prescription filling were also observed between the 4 age groups. For instance, the proportion of patients initially filling a prescription for metformin decreased steadily with increasing age (from 53% among the 18–34 year group to 27% among the ≥65 year group). In contrast, the proportion of patients initially filling a prescription for glyburide or immediate-release glipizide increased among older patients.

Overall Persistence and Persistence Across Demographic Groups
On average, the overall persistence across all oral hypoglycemic agents was 166.7 days. Persistence was significantly longer (11.6 days) among men than among women (172.6 days versus 161.0 days, \( P < 0.001 \)). There were consistent persistence differences among men and women for the individual drugs (Figure 1). Persistence significantly increased with age (\( P < 0.05 \)), reaching a peak among patients aged 50 to 64 years (125.1 days among those aged 18–34 years, 162.4 days among those aged 35–49 years, and 178.7 days among those aged 50–64 years), but then decreased to 161.4 days among those aged 65 years. Persistence was significantly higher among patients aged 50–64 years (125.1 days among those aged 18–34 years, 162.4 days among those aged 35–49 years, and 178.7 days among those aged 50–64 years), but then decreased to 161.4 days among those aged 65 years. Persistence by age and drug category is shown in Figure 2 and Table 2.

During the follow-up period, 13% of all patients switched from their initially assigned oral hypoglycemic drug treatment to one of the other 7 drug therapies. The repaglinide group and the immediate-release glipizide group had the highest turnover rates at 23% and 20%, respectively. Within the remaining drug categories, 12% to 15% of the patients switched away from their initial assigned treatment. Of patients that switched from any sulfonylurea (glimepiride, immediate-release glipizide, glipizide GITS, and glyburide), 40% switched to a biguanide (metformin) and 23% switched to a thiazolidinedione (pioglitazone and rosiglitazone). Of those patients that switched away from immediate-release sulfonylureas (glimepiride, glipizide, and glyburide), 19.4% switched to the extended-release sulfonylurea (glipizide GITS). When patients were switched from biguanide (metformin), they more typically were switched to one of the sulfonylureas (55.5%) or one of the thiazolidinediones (41.7%). Finally, of patients switched from the thiazolidinediones, 33.8%, 31% and 5.1% were switched to a sulfonylurea, biguanide, and meglitinide, respectively. Turnover from one thiazolidinedione to another was approximately 30%.

Persistence Across Drug Groups
The average length of therapy across the 8 oral hypoglycemic treatment groups is shown in Figure 3. Of all agents, repaglinide and immediate-release glipizide had the lowest persistence. Patients who initially filled immediate-release glipizide or repaglinide were significantly less persistent compared to patients who initially filled any other therapy (\( P < 0.05 \)) (Figure 3).

Patients treated with glipizide GITS persisted longer with their initial treatment than did patients treated with the other therapies. Statistically significant differences in length of therapy were seen for glipizide GITS versus metformin, glyburide, immediate-release glipizide, and repaglinide (\( P < 0.05 \)) (Table 3). Persistence with therapy for pioglitazone, rosiglitazone, and glimepiride was comparable to glipizide GITS (no statistically significant differences). The drugs with the largest difference in length of therapy were glipizide GITS and repaglinide, with an average difference of 51.2 days (\( P < 0.05 \)).

Persistence differences were also noted across sex and age categories within the various drug treatments. Women

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Table 1. Patient Demographics and Distribution of Initial Oral Hypoglycemic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age, n (%)</th>
<th>Sex, n (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>18–34 yr</td>
<td>35–49 yr</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>23 (3.6)</td>
<td>169 (28.1)</td>
</tr>
<tr>
<td>Glipizide IR (brand/generic)</td>
<td>15 (2.4)</td>
<td>112 (18.2)</td>
</tr>
<tr>
<td>Glipizide GITS (Glucotrol XL)</td>
<td>18 (2.8)</td>
<td>104 (16.8)</td>
</tr>
<tr>
<td>Glyburide (brand/generic)</td>
<td>20 (3.1)</td>
<td>124 (20.1)</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>20 (3.1)</td>
<td>115 (18.9)</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>18 (2.8)</td>
<td>119 (19.2)</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>18 (2.8)</td>
<td>120 (19.6)</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>17 (2.6)</td>
<td>123 (19.9)</td>
</tr>
<tr>
<td>Total</td>
<td>105 (16.2)</td>
<td>741 (12.2)</td>
</tr>
</tbody>
</table>

Note: Sex is not independent of treatment (\( \chi^2 = 98.47, df = 7, P < 0.0001 \)). Age is not independent of treatment (\( \chi^2 = 1269.14, df = 21, P < 0.0001 \)).

GITS = gastrointestinal therapeutic system; IR = immediate-release.
were less persistent than men for all drug treatments by a range of 8 to 17 days, and these differences were statistically significant within all treatment categories except for the glyburide and immediate-release glipizide groups ($P < 0.05$). Across age groups, differences in persistence were also observed (Figure 2). Of note is the variation in persistence across drug groups observed among the youngest age group (89 days) and the oldest age group (38 days).

Within the 35-to-49-year age group, immediate-release glipizide (134 days), glipizide GITS (173 days), and repaglinide (111 days) were significantly different from the age group average persistence of 162.4 days ($P < 0.05$). Within the 50-to-64-year age group, immediate-release glipizide (150 days) and repaglinide (123 days) were significantly different from the age group average of 179 days ($P < 0.05$). Within the $\geq 65$ years and older group, glipizide GITS (175 days) and repaglinide (137 days) were significantly different from the age group average of 161 days ($P < 0.05$). No significant differences within the 18-to-34-year age group were identified, probably due to small sample sizes.

**Discussion**

Lifelong treatment is usually necessary for persons diagnosed with type 2 diabetes. Lack of persistence with oral
hypoglycemic drug treatment likely signals failure in a patient’s management because of ineffectiveness, intolerance, and/or other factors. This study is the most current national evaluation of oral drug persistence in type 2 diabetes across a wide range of drug classes (including the sulfonylureas, biguanides, thiazolidinediones, and meglitinides). The results illustrate important issues and concerns with oral hypoglycemic drug persistence in patients newly starting oral medication for management of type 2 diabetes. Overall, patients did not seem to obtain adequate refills of their hypoglycemic medication, with medication available for only 167 out of 300 days. Furthermore, the largest differences in persistence were seen across drug therapies rather than within demographic groups. The relatively poor performance across all drug classes is a clear signal to the clinical community that patients newly diagnosed with type 2 diabetes do not remain on their treatment or do not refill their prescription so that they have medication available on a regular basis. In fact, the actual number of days with available medication in this study may have been even lower, as the study definition of persistence allowed lapses as long as 30 days in obtaining refills before the patient was considered nonpersistent. While this 30-day window to obtain refills may underestimate actual persistence, we selected this definition because it is commonly used in pharmacy claims analyses [14].

The clinical implication of poor persistence is a lack of glycemic control, poorer clinical outcomes, and ultimately higher costs. Previous studies have shown that nonadherent patients have higher mean blood glucose levels than adherent patients [11]. Within other diseases, poor refill compliance has been correlated with low drug serum levels and reduced clinical effect [16,17]. The current study results are both comparable to and expand on other analyses examining specific hypoglycemic agents. In a study using prescription claims information for Medicaid patients newly diagnosed with type 2 diabetes, mean days of immediate-release glipizide and glyburide supply obtained reached 157 days out of a maximum of 360 days (44%) [7]. In a study of newly diagnosed Medicaid patients younger than 65 years treated with glyburide, therapy obtained covered 210 days out of 360 days (58%) [8]. Most recently, another PBM claims analysis found 1-year persistence rates of 60% for metformin, 56% for sulfonylureas, and 48% for repaglinide [14]. Our study found similar persistence rates of 42% to 59%; however, it provides additional data on currently used thiazolidinediones as well as

Table 2. Average Length of Therapy for Age Groups by Oral Hypoglycemic Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Within Drug</th>
<th>18–34 yr*</th>
<th>35–49 yr</th>
<th>50–64 yr</th>
<th>≥ 65 yr</th>
<th>P Value (F, dfn, dfd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>172.3 ± 137.2</td>
<td>145.6 ± 127.1</td>
<td>163.5 ± 135.4</td>
<td>183.0 ± 138.5</td>
<td>168.2 ± 137.3</td>
<td>&lt; 0.05 (6.61, 3, 4665)</td>
</tr>
<tr>
<td>Glipizide IR (brand/generic)</td>
<td>149.3 ± 132.3</td>
<td>107.3 ± 118.3</td>
<td>133.7† ± 127.5</td>
<td>149.9† ± 132.0</td>
<td>154.6 ± 134.2</td>
<td>&lt; 0.05 (5.01, 3, 3137)</td>
</tr>
<tr>
<td>Glipizide GITS (Glucotrol XL)</td>
<td>176.9 ± 139.4</td>
<td>140.3 ± 126.7</td>
<td>172.9† ± 138.7</td>
<td>184.2 ± 139.7</td>
<td>174.8† ± 140.3</td>
<td>&lt; 0.05 (7.03, 3, 6932)</td>
</tr>
<tr>
<td>Glyburide (brand/generic)</td>
<td>163.2 ± 137.2</td>
<td>127.9 ± 123.1</td>
<td>157.4 ± 135.7</td>
<td>157.9 ± 139.7</td>
<td>160.8 ± 136.6</td>
<td>&lt; 0.05 (13.3, 3, 9711)</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>167.3 ± 138.7</td>
<td>119.7 ± 115.9</td>
<td>166.0 ± 137.5</td>
<td>183.2 ± 141.7</td>
<td>156.8 ± 139.3</td>
<td>&lt; 0.05 (70.6, 3, 16111)</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>174.5 ± 136.4</td>
<td>178.8 ± 128.3</td>
<td>171.9 ± 132.8</td>
<td>192.5 ± 138.2</td>
<td>155.8 ± 136.4</td>
<td>&lt; 0.05 (5.79, 3, 1181)</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>173.2 ± 136.8</td>
<td>124.6 ± 114.4</td>
<td>165.6 ± 135.0</td>
<td>186.2 ± 136.9</td>
<td>167.1 ± 138.8</td>
<td>&lt; 0.05 (10.5, 3, 3828)</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>125.8 ± 123.5</td>
<td>89.8 ± 104.2</td>
<td>111.3† ± 114.0</td>
<td>122.5† ± 120.4</td>
<td>136.6† ± 130.8</td>
<td>&lt; 0.05 (3.75, 3, 1287)</td>
</tr>
</tbody>
</table>

P value < 0.05 < 0.05 < 0.05 < 0.05 < 0.05
(F, dfn, dfd) (32.7, 7, 46876) (2.51, 7, 1572) (9.81, 7, 8833) (19.5, 7, 17106) (9.23, 7, 19341)

Average length of therapy across drugs

166.7 ± 137.3 125.1 ± 119.0 162.4 ± 135.8 178.7 ± 139.1 161.4 ± 137.8 < 0.05 (3.04, 3, 46880)

*Limited significance of pairwise differences among drugs in the 18–34 year age group likely due to small cell sizes.
†Test wise statistically significant from average across drugs at alpha = 0.005 so that family wise error of alpha < 0.05 (t critical value = 2.576).
GITS = gastrointestinal therapeutic system; IR = immediate-release.
examines the individual sulfonylureas. Interestingly, our study found significant differences in persistence within the sulfonylurea class. Nevertheless, these previous studies, along with the current results, confirm that the overall hypoglycemic medication persistence is low among patients newly diagnosed and treated for type 2 diabetes.

Sex and Persistence
It has been suggested that women have better adherence to chronic drug treatment as they are more sensitive to illness, more willing to seek health care, use more health care, and in general have a greater responsibility for family health [18]. Surprisingly, women in our study were actually found to be somewhat less persistent (by approximately 12 days) than men almost consistently across all the oral hypoglycemic treatments evaluated. This finding, though unusual, is supported by findings of several prescription refill adherence studies in different diseases [16,19]. To the contrary, Sclar and colleagues reported newly diagnosed women receiving Medicaid to be more than twice as likely to persist with oral hypoglycemic therapy than men [7]. Other diabetes studies, using different adherence measurement methods, have found no significant difference by sex [11,18]. Similar results are found in oral treatment adherence studies within hypertension and hyperlipidemia [20–25]. Clearly, the literature does not show a consistent association between sex and persistence.

Age and Persistence
This study demonstrates that persistence is the lowest in young patients and increases with age to a peak in patients 50 to 64 years of age, before declining among patients aged 65 years and older. Some studies of type 2 diabetes find that as age increases, so does adherence to the oral antidiabetic drug treatment regimen [7,11]. On the contrary, older age was not a significant predictor of oral hypoglycemic drug treatment adherence in a study where adherence was self-reported [26]. With respect to age and persistence in other chronic, initially asymptomatic diseases, increased age has been found to be associated with increased drug treatment adherence in newly diagnosed hypertension and dyslipidemia [20–22,25,27]. Again, however, a number of other studies within these diseases report no significant association between age and adherence [19,28,29]. The potential for coexisting diseases and related polypharmacy in elderly patients may help explain the significant fall in persistence that we observed in the ≥65-year age group; however, the specific data set did not allow us to confirm this hypothesis.

Drug Treatment and Persistence
The largest differences in persistence were seen across drug therapies rather than within demographic groups. This finding is important given that clinicians cannot control the age or sex of their patients but do have many choices with regard to the initial hypoglycemic therapy. Average persistence differences
across all age groups were as high as 51 days. Within age groups, the differences were even larger. An example of this is seen in the 18-to-34-year age group, where differences in persistence were as high as 89 days (179 days for pioglitazone versus 90 days for repaglinide).

Although these data do not permit an analysis of reasons for discontinuation, one could hypothesize that these persistence differences may be partially explained by the side effect profiles of the drugs and to some extent the complexity of the treatment regimen. The agents with the highest persistence rates were those generally given once daily and that have relatively low rates of bothersome adverse events (eg, minimal/low gastrointestinal disturbances and hypoglycemia). Specifically, patients persisted longer on glipizide GITS, pioglitazone, rosiglitazone, and glimepiride as compared to glyburide, immediate-release glipizide, and repaglinide.

Hypoglycemia may be an important factor associated with the poor persistence with glyburide and immediate-release glipizide therapies, often the most common side effect experienced by patients on these agents and the most common reason for discontinuation of these drugs [30]. Clinical trials have found that mild to moderate hypoglycemia occurred in 20% of glyburide and 19% of immediate-release glipizide patients [31]. In natural settings, the prevalence of hypoglycemia may be twice as high for patients on glyburide as for patients being treated with immediate-release glipizide [32,33]. Despite these reported differences, this study found that patients treated with glyburide stayed approximately 14 days longer on treatment compared with patients treated with immediate-release glipizide.

The results regarding persistence of therapy cannot be explained by side effects alone, however. Even though repaglinide has a favorable side effect profile, it was the only agent that has to be taken with meals (typically resulting in 3 administrations per day), which may have contributed to it having the lowest persistence among the therapies evaluated. These findings may highlight the importance of extended-release or once-daily formulations, which have been suggested to improve medication-taking behavior and also to partially compensate for delays and gaps in proper dosing [34]. Reducing the dosing frequency is an important factor to achieve increased oral hypoglycemic drug adherence. In studies where adherence was measured by pill counts or refill behavior, there were associations or trends supporting the fact that reduction of the dosing frequency improved persistence [13]. Similarly, a significant positive association between a lower frequency dosing regimen and drug treatment adherence has been identified in other chronic diseases [19,22,27,28].

Limitations
This study presents preliminary results that suggest trends in persistence differences across treatment categories. We attempted to define the inclusion/exclusion criteria such that the analysis population would represent a general type 2 diabetes population, most likely those initiating oral therapy after lifestyle modifications have failed. However, pharmacy claims database research is limited for a number of reasons and must be interpreted with caution. Nevertheless, pharmacy claims analyses often give valuable insights to the real-world use of drug therapies and provide hypotheses for future research. In the present study, we were able to remove obvious confounders, such as variations in the number of days medication was supplied and changes in insurance

### Table 3. Differences in Average Days of Therapy of Index Drug versus Comparative Drug

<table>
<thead>
<tr>
<th>Index Drug</th>
<th>Glipizide GITS (Glucotrol XL)</th>
<th>Pioglitazone (Actos)</th>
<th>Rosiglitazone (Avandia)</th>
<th>Glimepiride (Amaryl)</th>
<th>Metformin (Glucophage)</th>
<th>Glyburide (brand/generic)</th>
<th>Glipizide IR (brand/generic)</th>
<th>Repaglinide (Prandin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide GITS (Glucotrol XL)</td>
<td>—</td>
<td>2.46</td>
<td>3.72</td>
<td>4.61</td>
<td>9.70*</td>
<td>13.7*</td>
<td>27.64*</td>
<td>51.20*</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>—</td>
<td>—</td>
<td>1.26</td>
<td>2.15</td>
<td>7.24</td>
<td>11.26</td>
<td>25.18*</td>
<td>48.74*</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>—</td>
<td>0.89</td>
<td>5.98</td>
<td>9.99*</td>
<td>23.9*</td>
<td>47.48*</td>
<td>23.92*</td>
<td>47.48*</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>—</td>
<td>—</td>
<td>5.09</td>
<td>9.11*</td>
<td>23.04*</td>
<td>46.59*</td>
<td>47.48*</td>
<td>47.48*</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>—</td>
<td>—</td>
<td>4.02</td>
<td>17.95*</td>
<td>41.50*</td>
<td>47.48*</td>
<td>41.50*</td>
<td>47.48*</td>
</tr>
<tr>
<td>Glyburide (brand/generic)</td>
<td>—</td>
<td>—</td>
<td>13.9*</td>
<td>37.48*</td>
<td>—</td>
<td>37.48*</td>
<td>37.48*</td>
<td>—</td>
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<tr>
<td>Glipizide IR (brand/generic)</td>
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<tr>
<td>Repaglinide (Prandin)</td>
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</table>

*Differences in average duration of therapy (index drug minus comparative drug) significant at the 0.05 level.

GITS = gastrointestinal therapeutic system; IR = immediate-release.
coverage. Changes in insurance coverage is an important issue for persistence studies, and we included only those patients with continuous drug insurance coverage from the entire pre-period through the entire timeframe of the analysis; the number of days supplied was also uniform in the cohort.

Because underlying reasons for differences in persistence, such as severity of type 2 diabetes and concomitant diseases, could not be examined, selection bias is possibly present. Specifically, systematic differences in patient characteristics could conceivably exist across the drug treatment groups, which might affect the persistence ratio and interfere with the interpretation of the comparison across treatment categories. In addition, calculation of persistence based on number of days supplied may be a limitation, as it does not reflect changes in the use of medication on verbal instruction from the physician (eg, patients may be incorrectly classified in the analysis as not persistent if they reduce the dose of their medication to a half tablet once daily instead of a whole tablet).

A key limitation common to most pharmacy claims database analyses is the lack of additional clinical information regarding both patient and physician reasons for changes in therapy. It would also be of interest to evaluate the association between oral hypoglycemic drug persistence with actual hemoglobin A1c levels to assess whether high drug persistence is correlated with controlled blood glucose. In addition, future research could also include development of the clinical pathways for patients starting oral agents to determine what agents are added as second and third line therapies.

Another consideration with any pharmacy claims analysis is defining an adequate preperiod to ensure that new medications truly represent a new treatment for the patient. It would also be of interest to evaluate the association between oral hypoglycemic drug persistence with actual hemoglobin A1c levels to assess whether high drug persistence is correlated with controlled blood glucose. In addition, future research could also include development of the clinical pathways for patients starting oral agents to determine what agents are added as second and third line therapies.

In addition, the economic, psychosocial, and behavioral factors that play a role in drug adherence were not addressed due to absence of such data. However, it is interesting to note that patients in the 65 year and older age group were receiving more of the generic sulfonylureas than the other age groups. This may indicate that there was some selection bias related to drug affordability issues (lower copayments for generic agents). In addition, this analysis could not assess patients with public insurance coverage only (eg, Medicaid or Medicare only).

From the psychosocial and behavioral aspect, the overall low treatment persistence found in this study may partly be explained by the fact that the cohort likely consists of newly diagnosed patients who may be more likely to switch therapies (until a tolerable agent is found) and/or just simply be nonadherent to their prescribed treatment (patient is in a newly diagnosed, contemplation stage and not actively taking responsibility for their disease). These findings may not be surprising given that persistence is poor within other chronic diseases such as hypertension, particularly for newly diagnosed patients [23,27]. Caro and colleagues reported that patients newly diagnosed with hypertension persisted significantly less with their oral drug treatment at the end of 1 year compared to patients with ongoing hypertension (persistence rates of 78% versus 97%, respectively) [23].

Finally, examining prescription refill behavior provides information on whether patients purchase their medications but not whether the patients are using them [35]. Nevertheless, we have no basis to believe that use varies differently from purchase (and therefore intended use). Adherence is secondary to availability, since it is impossible for patients to be persistent or adherent with a treatment regimen without having the drug available.

Conclusion

Overall persistence with the initial oral hypoglycemic drug treatment is suboptimal in patients with type 2 diabetes. Differences in hypoglycemic treatment persistence exist across sex, age, and individual drug categories. These differences appear to be associated with initial drug choice rather than with patient age or sex. Careful selection of the initial hypoglycemic agent to minimize adverse events and reduce dosing frequency may improve persistence, enhance glycemic control, and reduce the economic burden of type 2 diabetes.

The results of this study may be useful for educating clinicians about the lack of persistence with the initial oral medication in type 2 diabetes and serve as an impetus to enhance patient self-management education programs. Self-management education programs should consider incorporating additional follow-up regarding the importance of adhering to a prescribed treatment. Future research should examine the impact of oral hypoglycemic drug persistence on achieving good glycemic control across age, sex, and drug classes.

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References


