Using Pharmacy Claims Data to Study Adherence to Glaucoma Medications: Methodology and Findings of the Glaucoma Adherence and Persistency Study (GAPS)

David S. Friedman,1,2 Harry A. Quigley,1 Laurie Gelb,3 Jason Tan,3 Jay Margolis,3 Sonali N. Shab,4 Elizabeth E. Kim,1 Thom Zimmerman,5 and Steven R. Hahn1,6,7

PURPOSE. To develop methods for investigating adherence to glaucoma medications by using a modified claims data-based measure of adherence, validation by chart review, and patient and physician interviews.

METHODS. Data from administrative claims of 13,956 subjects receiving an initial glaucoma medication, and data from overlapping samples of 300 patients’ charts, 300 interviews of patients, and 103 interviews of physicians were analyzed and compared.

RESULTS. The mean medication possession ratio (MPR) was 0.64 (median 0.57) for the 13,956 subjects. Although 59% potentially had an ocular hypotensive agent at 12 months, only 10% had such medication available continuously. Chart review revealed that 31% of subjects “new to therapy” in claims data had actually been previously treated; and that 90% of the 17% who had medication added to initial monotherapy were misclassified by claims-based algorithms as medication switches or no change. Twenty percent of surveyed patients received samples on a regular basis and had lower MPR than those who did not (P < 0.05).

CONCLUSIONS. Large pharmacy databases offer insight into medication usage but are vulnerable to errors from sampling (since patients who receive samples will be considered to have poor adherence), misidentification of newly treated patients, and misclassification of added versus switched medications. That a large proportion of patients stop and restart medications makes MPR a robust measure of adherence over time that reflects the resumption of medication after a gap in adherence. The data confirm that adherence to treatment with glaucoma medications is poor, similar to adherence in patients with other chronic diseases. (Invest Ophthalmol Vis Sci. 2007;48: 5052–5057) DOI:10.1167/iovs.07-0290

On average, patients with chronic medical conditions take from 30% to 70% of the prescribed medication doses and on average 50% discontinue medications in the first months of therapy.1 The ophthalmic literature shows similarly low rates of adherence to treatment.2 The present study, the Glaucoma Adherence and Persistency Study (GAPS), is an attempt to increase our understanding of the determinants of adherence in the use of topical glaucoma medications. GAPS used four overlapping and converging sources of information to study adherence. The first was a retrospective pharmacy claims database of almost 14,000 patients prescribed topical ocular hypotensives; the second was a telephone survey of 105 physicians who were among the most active in prescribing these medications in that database; the third was a telephone survey of 300 patients from that database (all of whom gave oral consent), 115 of whom were patients of the surveyed physicians; and the fourth was a review of the charts of 300 patients, 225 of whom were also participants in the patient survey, and 74 of whom were patients of the surveyed physicians, but not participants in the patient survey (Fig. 1). To interview the targeted 100 physicians, 436 physician’s offices were contacted. Eighteen physicians were ineligible due to death or retirement or had practices that did not treat glaucoma, and an additional 140 physicians were not reachable during the fielding period, most often due to lack of current contact information. Of the 241 physicians who were reached and reconrmed that they treat glaucoma, 106 expressed interest in the study and 103 were interviewed, for a response rate of 44% among those physicians contacted.

Determining adherence to medical regimens can be challenging. The present report describes the development and characteristics of methods used to analyze the pharmacy claims data that provided the primary measure of adherence used in GAPS and to quantify adherence in this cohort of patients with glaucoma.

METHODS

The research was performed with Institutional Review Board approval at Johns Hopkins University and by Quorum Review in accordance with the Declaration of Helsinki and in compliance with regulations of the Health Insurance Portability and Accountability Act (HIPAA).

Computation of Medication Possession Ratio

The medication possession ratio (MPR) is defined as the days of prescription supply dispensed divided by the number of days between the first and last prescription refill (Appendix 1; all appendices are online at http://www.iovs.org/cgi/content/full/48/11/5052/DC1). For this study, we consulted the literature regarding the average bottle volume and drop count, to determine the days of supply of drops in dispensed medications. We then calculated the expected duration of the medication in bottles of the various glaucoma eye drops3 to determine the MPR.4–6

From the 1Wilmer Eye Institute, Baltimore, Maryland; the 2Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; 3HealthCore, Inc., Wilmington, Delaware; 4Pfizer Inc., New York, New York; the 5Department of Ophthalmology and Visual Sciences, University of Louisville School of Medicine, Louisville, Kentucky; the 6Albert Einstein College of Medicine, Bronx, New York; and the 7Medintel On-Call, Pleasantville, New York.

Supported by an unrestricted grant from Pfizer Inc.

Submitted for publication March 9, 2007; revised June 8, 2007; accepted August 28, 2007.

Disclosure: D.S. Friedman, Pfizer and Alcon (F, R, C); H.A. Quigley, Pfizer and Alcon (C, R); L. Gelb, None; J. Tan, Pfizer (F); J. Margolis, None; S.N. Shah, Pfizer (E); E.E. Kim, Pfizer (E); T. Zimmerman, Pfizer (C, R); S.R. Hahn, Pfizer (C, R)

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: David S. Friedman, 600 North Wolfe Street, Wilmer 120, Johns Hopkins Hospital, Baltimore, MD 21287; david.friedman@jhu.edu.


Copyright © Association for Research in Vision and Ophthalmology

5052
Gap Analysis of Patterns of Use of Index Medication

For the gap analysis, patients were classified as “persistent”—that is, without a “gap” in their use of prostaglandin medication—if they refilled the medication within 60 days if their last dispensed quantity was a 2.5-mL bottle, within 90 days if a 5-mL bottle, and within 120 days if a 2.5-mL bottle. Subjects who were persistent with their index (initial) prostaglandin medication were further classified as persistent in monotherapy on the index prostaglandin or as persistent with add-on medication if an additional medication was added during the observation period. Subjects who were not persistent with their index prostaglandin were further classified as “restart” if they received another prescription for the same index medication after a gap as just specified, or as “switch” if they received a different medication and no further refills of the index medication.

Database

The HealthCore Managed Care Database (Wellpoint, Inc., Wilmington, DE) provides retrospective insurance claims data with access to medical charts, physicians, and patients for conducting HIPAA-compliant research. The database contains a geographically diverse sample of longitudinal claims data from health plans in the Southeastern, Mid-Atlantic, Central, and Western regions of the United States from January 1, 1999. As of initiation of the retrospective analysis in September 2005, these health plans had approximately 24.8 million members with complete capture of medical, pharmacy, and healthcare provider encounters for approximately 12.9 million members. The database reflects various commercial plan designs (e.g., health maintenance organization, preferred provider organization, and point of service). The study cohort was drawn from individuals with sufficient claims data for analysis from January 1, 1999, through August 31, 2005, and who met the other inclusion criteria described.

Data used in this report were derived from four data sources. First, the claims data on coded diagnoses, visits, diagnostic testing, and prescription filling were retrospectively analyzed. Second, 103 physicians in the database, selected from among those who had the most patients using a medication of interest, were interviewed by telephone about their glaucoma-related beliefs and clinical practices. Third, 300 patients, 115 of whom were patients treated by the surveyed physicians, were interviewed by telephone about their knowledge of glaucoma, their interaction with the treating physician, and their medication usage. Fourth, charts of 225 of the interviewed patients and an additional 75 patients were abstracted in detail for diagnosis, clinical findings, medication prescription history, side effects, and interactions between physician and patient. A description of the data sources used in this analysis is provided later.

Subject Selection: Retrospective Analysis

Patients selected for retrospective analysis had to have filled a prescription for an ocular hypotensive agent (Appendix 3) between May 1, 2001, and November 30, 2004. The date of the first prescription for a medication of interest filled during this period was considered the index date.

In an attempt to select only newly treated patients, study subjects were excluded if they had been treated with any of the ocular hypotensive medications (including any excluded medications) during the 6-month “preindex period” (before the patient’s index date). Furthermore, study subjects could not have had a glaucoma procedure such as laser trabeculectomy or trabeculectomy (procedures listed in Appendix 4) during the 6-month preindex period. For the purposes of this report, we also evaluated how the study population changed when we extended the exclusion period to 12 months for both medications and procedures.

Subjects were excluded if they filled a prescription for any topical glaucoma medication other than the index medication on or within 30 days after their index date. Subjects were required to have had a

**Days of Supply per Bottle**

The number of drops per bottle of medication was determined from the only published study available or from the manufacturer’s estimates for products not addressed in that publication (Appendix 2). We assumed bilateral eye drop use for all patients, once-daily use of prostaglandins and gel-forming timolol, and twice-daily administration of all other medications. We assumed bilateral eye drop use for all patients, once-daily use of prostaglandins and gel-forming timolol, and twice-daily administration of all other medications (β-blockers, α-adrenergic agonists, and carbonic anhydrase inhibitors). The number of drops required per day was calculated by multiplying the daily frequency by two (assuming 1 drop in each eye per day). The number of days for each product size was computed by dividing the stated number of drops in a container by the drops per day. For patients on monotherapy, the numerator for MPR was the number of days of drug available per bottle for each bottle of medication obtained from the index date to the end of the patient’s observation period. The end of the observation period was the earlier of the first postindex date of any glaucoma surgery (laser trabecuoloplasty, laser or surgical iridotomy, trabeculectomy, glaucoma shunt device placement or revision, or ablation of the ciliary body) or the date of the end of enrollment in a participating health plan.

Combination therapies were recognized when drug A was followed by drug B from a different drug class and when drug A (or another drug from the same drug class as drug A) was refilled on or after the start date of drug B. Drug B was then assumed to be added to the regimen. Although there are patients in whom drug B is discontinued at the request of the physician (due to ineffectiveness or side effects), it was assumed that this is not usually the case with glaucoma combination therapy and therefore that drug B was expected to be instilled regularly from that point forward. If a third drug, drug C, was filled in a different class than drugs A and B, it was considered a third drug in the combination. In combination therapy, the MPR denominator was the sum of the days of supply required for every drug in the regimen.

An MPR greater than 1 can occur for many reasons, some reflective of adherence intention and some not. For example, an MPR > 1.0 could be reached if subjects intentionally or inadvertently use more than 1 drop when instilling medication (resulting in a more frequent need for refills), if they hoard or stockpile medication (e.g., obtain early refills for financial reasons or travel), or if they lose a bottle. Subjects may also mistakenly refill a prescription from which the physician has recommended they switch or may switch medications while they still have a supply of their original drops.
diagnosis code signifying open-angle glaucoma (complete list in Appendix 5) on a medical claim between 6 months before their index date (preindex period) or within 12 months after their index date (postindex period). Subjects had to be 40 years of age or older on the index date and had to have continuous enrollment in a health plan for at least 6 months preceding the index date and for a minimum of 3 months after index. The postindex observation period was censored if the subject changed health insurer.

Subject Selection: Physician Survey

We targeted physicians with the largest number of subjects in the database to assess associations between physician characteristics and the patients’ behavior. Beginning in October of 2005, we attempted to contact 436 physicians, succeeded in contacting 241 who confirmed that they treat glaucoma, and completed interviews with 103 regarding the characteristics of their offices, their glaucoma-related beliefs, and their treatment strategies. Eighty-seven of the surveyed physicians had four or more patients in the retrospective pharmacy claims database.

Subject Selection: Patient Survey

Recruitment for the patient survey sought to include 300 patients, each of whom had initiated therapy on one of the three prostaglandins and to include as many patients as possible from among the 103 physicians interviewed in the study. To accomplish this, the physicians were ordered on descending volume of patients with primary open-angle glaucoma in the HealthCore database who were eligible for retrospective analysis.

Attempts were made to contact 2651 of the 4984 whose index medication was a prostaglandin, 909 of whom were contacted. Information obtained during that contact disqualified 49, and 545 were contacted and willing to participate. A coding error causing missing data required exclusion of 12 of the first 300 subjects, who were replaced with a similar number of subjects, resulting in the final sample of 300 surveyed subjects. Telephone surveys of the patients began in October 2005.

One hundred fifteen eligible persons who were patients of surveyed physicians were recruited. The remaining surveyed patients were not matched to a surveyed physician. Sixty-two of the surveyed physicians contributed from one to five of the surveyed patients. The final sample included 106 patients taking latanoprost, 104 on bimatoprost, and 90 on travoprost. All prostaglandins required a copay. Latanoprost and bimatoprost were tier 2, requiring the lowest branded product copay in all plans. In some plans, however, travoprost was a tier 3 medication requiring a higher copay; 56% of the patients included in the sample had one of these plans.

We attempted to enroll patients who had a minimum of 6 months of plan eligibility before the index date and succeeded in enrolling 236 surveyed subjects who had at least 12 months of eligibility. However, 64 subjects had at least 3 but fewer than 12 months of eligibility. Patients were interviewed a mean of 2.73 ± 1.03 years after the date of the index prescription in the pharmacy claims database and a mean of 3.59 ± 1.68 years after the first charted glaucoma prescription noted in the 225 patients whose charts were also reviewed.

Medical Chart Abstraction

The charts of all 300 surveyed patients were requested for abstraction. When a chart could not be obtained for an interviewed patient, then a chart from another patient with the same index medication in the retrospective analysis was obtained. The charts of 225 were obtained, and the charts of 75 nonsurveyed patients, selected so as to maintain an equal number of persons started on each of the three prostaglandins and cared for by the interviewed ophthalmologists, were abstracted to achieve the goal of 300 chart reviews. Only 48 of the 300 chart-abstracted patients had fewer than 12 months of postindex claims eligibility. Patients whose charts were abstracted were slightly younger than those in the full cohort (64.45 ± 10.91 years vs. 65.94 ± 12.48 years; P = 0.04) and had higher MPRs (0.68 ± 0.40 vs. 0.63 ± 0.42; P = 0.03).

Medical Comorbidities

To determine whether co-occurring medical illnesses might be a factor in adherence, we performed a preliminary assessment using the Deyo-Charlson comorbidity scoring index, a numerical score computed as the weighted sum of any co-occurring diagnoses.7

RESULTS

A total of 13,977 persons met eligibility criteria for inclusion in the retrospective pharmacy claims analysis, 21 of whom were censored due to glaucoma surgery within 3 months of the index date. The pharmacy claims for the remaining 13,956 had a mean follow-up of 22 months and a mean MPR of 0.64, with a median MPR of 0.57 (range, 0.01–3.7; Fig. 2).

Among 10,260 subjects who were followed up for at least 1 year after the index prescription, to measure persistency as a function of gaps between refills, 10% used the originally prescribed prostaglandin without any gaps in refilling the prescription, 8% as monotherapy, and 2% with a second drug added to their regimen. Slightly more than half (54%) of the subjects had a gap in refilling the index drug but restarted after the gap; 22%
of these (or 12% of the original 10,260) remained persistent after restarting, and 78% (or 42% of the original group) had at least one more gap after restarting. Sixteen percent switched from the index drug to another drug, and 20% discontinued all medications after restarting. Sixteen percent switched after restarting, and 78% (or 42% of the original group) had at least one more gap after restarting. Sixteen percent switched after restarting, and 78% (or 42% of the original group) had at least one more gap after restarting. Sixteen percent switched after restarting, and 78% (or 42% of the original 10,260) remained persistent after restarting.

Surveyed patients were 1.9 years younger on average than the patients in the pharmacy claims database ($P = 0.01$). They were more likely to be women (65.7% vs. 56.2%, respectively; $P < 0.01$) and to have a high MPR (mean, 0.67 ± 0.38 vs. 0.63 ± 0.42, respectively; median, 0.61 vs. 0.56, respectively; $P = 0.04$). Based on chart data, nearly 17% of patients were using ocular hypotensive drops in only one eye (Table 1). The mean MPR was 0.56 for these subjects, as opposed to 0.70 for subjects using medications bilaterally ($P = 0.03$).

Despite the required absence of glaucoma medication in the medical and pharmacy claims database in the preindex period, 34.7% of the subjects whose charts were surveyed had received a prior diagnosis and 31.0% had been treated with ocular hypotensive agents. To assess further the ability to identify subjects with newly diagnosed glaucoma using claims data, we examined the charts of the 242 subjects with no glaucoma treatment or diagnosis codes for 12 months before the index prescription. Even in these subjects, chart review revealed that 24% had received a prior diagnosis and 27.3% had been treated.

In this study, we did not choose a days-of-persistency survival curve analysis as our principal metric, because it does not consider all the refilling behavior across the observation period. More than 55% of the patients who had at least 1 year of follow-up, failed to continuously refill their initial medications for a period and later restarted it. When using survival analysis, one must either ignore the adherence pattern during a substantial proportion of the observation period (i.e., after restarting), or one must perform separate subgroup analyses to study adherence by those who restart medication after stopping. In this study, a survival analysis would have identified 90% as failing to refill medications continuously over the study period. However, a large number of these individuals restarted their medications after a gap. MPR captures adherence over the entire observation period. In fact, the MPR of restarters had a survival curve analysis as our principal metric, because it does not consider all the refilling behavior across the observation period. More than 55% of the patients who had at least 1 year of follow-up, failed to continuously refill their initial medications for a period and later restarted it. When using survival analysis, one must either ignore the adherence pattern during a substantial proportion of the observation period (i.e., after restarting), or one must perform separate subgroup analyses to study adherence by those who restart medication after stopping. In this study, a survival analysis would have identified 90% as failing to refill medications continuously over the study period. However, a large number of these individuals restarted their medications after a gap. MPR captures adherence over the entire observation period. In fact, the MPR of restarters had a mean of 0.55, a median of 0.60 ± 0.34, and range of 0.03 to 3.25, indicating considerable heterogeneity within this group.

**Table 1.** Monocular versus Binocular Medication Prescriptions from Chart Review

<table>
<thead>
<tr>
<th>Type of Glaucoma</th>
<th>Patients</th>
<th>MPR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>50</td>
<td>0.56</td>
</tr>
<tr>
<td>Bilateral</td>
<td>244</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*$P = 0.03$ for the difference between unilateral and bilateral therapy.

**Table 2.** Comparison of Claims Analysis and Chart-Based Classification of Medication Change

<table>
<thead>
<tr>
<th>Claims Database Classification</th>
<th>Chart Notation Classification</th>
<th>No Change n (%)</th>
<th>Add n (%)</th>
<th>Switch n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>105 (98.1)</td>
<td>7 (23.3)</td>
<td>4 (10.8)</td>
<td>116 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Add a medication</td>
<td>0 (0.0)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Switch to different medication</td>
<td>2 (1.9)</td>
<td>20 (66.7)</td>
<td>33 (89.2)</td>
<td>55 (31.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>107 (61.5)</td>
<td>30 (17.2)</td>
<td>37 (21.2)</td>
<td>174 (100)</td>
<td></td>
</tr>
</tbody>
</table>

The accuracy of the claims-based algorithms used to distinguish the addition of a new medication (add-on) from a switch to a new medication was assessed by comparing classification based on claims data with the physicians’ charted notations (Table 2). The comparison was performed for the 174 patients for whom the index medication was the most recent prescription before the chart review. Overall, 81% of prescription patterns were correctly classified by the database analysis, and most switch (89.2%) and no-change patients (98.1%) were also correctly classified.

Review of the 174 charts represented in Table 2 indicated that 17% of patients received a second medication that was intended to be used along with the initial drug (add-on). Pharmacy claims accurately identified patients whose medications were switched or did not change. However, only 10% of add-ons were correctly identified; 66.7% were misclassified by the pharmacy claims algorithm as switches and 23.3% were misclassified as no change.

**DISCUSSION**

Recent clinical trials confirm that ocular hypotensive therapy helps to preserve visual fields in patients with glaucoma. Poor adherence to ocular hypotensive medications therefore limits the effectiveness of the most common treatment for preventing vision loss from glaucoma. Pharmacy and medical claims data offer the unique power of very large samples, but demand a careful and sophisticated approach to measurement and interpretation. To meet this challenge, we developed a methodology that addresses key problems in pharmacy claims analysis to improve the accuracy of these metrics. The principal features of this methodology include the decision to use the MPR rather than a survival curve as the principal metric for persistency; calculation of MPR by using actual bottle contents to define days of supply; requiring evidence of a glaucoma diagnosis code before the first prescription, to exclude persons who may be prescribed ocular hypotensives for short-term use; and adjustment of MPR calculations for add-ons and switches.

For this study we did not choose a days-of-persistency survival curve analysis as our principal metric, because it does not consider all the refilling behavior across the observation period. More than 55% of the patients who had at least 1 year of follow-up, failed to continuously refill their initial medications for a period and later restarted it. When using survival analysis, one must either ignore the adherence pattern during a substantial proportion of the observation period (i.e., after restarting), or one must perform separate subgroup analyses to study adherence by those who restart medication after stopping. In this study, a survival analysis would have identified 90% as failing to refill medications continuously over the study period. However, a large number of these individuals restarted their medications after a gap. MPR captures adherence over the entire observation period. In fact, the MPR of restarters had a mean of 0.55, a median of 0.60 ± 0.34, and range of 0.03 to 3.25, indicating considerable heterogeneity within this group.
This variation would all be reduced to the value of the initial days of persistency, a limitation of survival curve analysis. A second reason for using MPR rather than survival analysis is the complexity of calculating an overall adherence metric when treatment regimens include more than one medication. When a patient fills prescriptions at the appropriate time without a gap for one medication but fails to do so with a second or third, the patient is either defined as failing to adhere because of the gap, or is defined as adherent, ignoring the nonadherence. By contrast, MPR adjusts for combination therapy and provides a single number to reflect the imperfect adherence to the combination of medications that have been prescribed. It also more reliably “restarts the clock” when a subject who has not used medication regularly has a partially used bottle on hand when she or he re-presents to a physician and subsequently fills a “new prescription.”

The importance of the choice between using a survival curve analysis-based days of persistency versus MPR metric is indicated by the observation that these two had a significant but modest correlation of 0.34 (Pearson’s correlation coefficient).

This study used health insurance claims data as the key source of information about patients’ adherence. Claims provide a complete listing of reimbursed services for a large insured population, but the accuracy of diagnostic information and the timing of drug exposure information must be considered with caution. Fulfillment of a prescription at the pharmacy does not ensure that the patient used the drug, and samples given by the physician do not appear in the claims data. Some patients may have had more than one health insurance provider and filled one or more prescriptions using other or no insurance. For patients who fill prescriptions but do not use the drops as prescribed, pharmacy claims metrics will overstate the true adherence to treatment. If patients fill prescriptions outside of the plan or use samples, adherence estimates will be lower than actual use.

Although claims-based classifications of patients whose medications were switched or not changed proved to be accurate based on comparison with charted data, misclassification of medication additions as switches may have occurred in approximately two thirds of the 17% of subjects whose physicians added medications to their regimens because a refill for the first drug did not appear in the claims data. This claims pattern may have two causes: (1) patients mistakenly believed that the second medication should replace the first; or (2) refill of the first drug was delayed because the patient had a large supply of it on hand due to previous nonadherence. Regardless of cause, this misclassification inflates MPR and therefore may obscure poor adherence in an important cohort: those patients whose physicians added medication to treat chronically elevated IOP that was due to undetected nonadherence rather than lack of treatment efficacy. The latter was the most commonly charted reason for medication changes. Indeed, in the physician survey component of this study, physicians commented that persistent IOP elevation was often a marker of nonadherence but also reported that they were often unable to distinguish true medication failures from nonadherence (data not presented). This speculation is also supported by a study of patients with “treatment-resistant” arterial hypertension who were subjected to complex polypharmacy. Subsequently, the use of an adherence-monitoring device showed that “treatment resistance” was actually due to nonadherence in 50% of subjects, including 30% who were “cured” because they became fully adherent, to the point of several syncopal episodes due to hypotension.

Assumptions about the use of combination therapies may have affected estimates of MPR. Some second- and third-line drugs may have been used for a brief period after they were stopped with the advice of the physician. If this were the case, we underestimated MPR in some patients. In addition, our assumption that some drugs that are recommended for three-times-per-day dose regimens (brimonidine and brinzolamide) were typically taken twice daily may have overestimated MPR if patients actually were intended to have enough drug for three-times-daily doses. The opposite is true of patients who may have been prescribed β-blockers once a day. Though these factors may affect the overall estimates of adherence, we believe that they should not affect the direction and magnitude of associations with factors influencing adherence.

Distribution of drug samples to patients typically occurs at the beginning of therapy. Some patients, often those for whom copays are a greater financial burden, use samples more extensively. Mathematically, one would expect that the more samples that a patient receives, the lower their MPR will be because the samples are not recorded in the claims database and therefore do not enter the numerator of the MPR calculation. However, the mean MPRs observed in patients who received samples one or more times or on a more regular basis (0.62 and 0.64, respectively) were not substantially lower than that of all surveyed patients (0.64). In contrast, patients who said they never received samples had a much higher MPR (0.76) than the other two groups and the surveyed sample mean. Whether this is due to a difference in patient attitude and/or physicians’ perceptions that the never-sampled subjects may not have needed samples to reinforce adherence cannot be determined with pharmacy claims analysis.

Another potentially significant consequence of providing samples when initiating treatment is the exclusion from pharmacy claims databases of patients who experience intolerable adverse effects or other critical barriers to adherence while taking the initial sample. These subjects will not generate even one prescription for the poorly tolerated drug or any prescription at all if they discontinue treatment altogether and therefore will not be captured in the database. Alternatively, some may fill a single prescription and then be told to stop using the medication due to lack of efficacy (which would overestimate lack of adherence). However, this was not seen in the chart reviews performed in this study. The duration of a bottle of eye drops is also a source of potential inaccuracy when estimating adherence. In calculating days of supply we have assumed that patients use only 1 drop every time they administer medicine, and this is likely not to be true in all cases. Anecdotally, many patients report putting more than 1 drop in the eye to be certain that the drop has been administered and some lack manual control over the number of drops dispensed. For these patients the MPR may be overestimated. If these patients refill when the bottle is empty, they will appear to have more drug available than they actually need. Alternatively, these patients may only refill on a monthly schedule, which would lead to a high MPR, but would fail to reflect the fact that the amount of drug was inadequate for the patient to administer it on a daily basis. In contrast, for the nearly 20% of patients prescribed monocular therapy (based on the chart review), the MPR is an underestimate because these patients are assumed to require more drugs than they actually need. Indeed, the MPR for this group was lower than for those on binocular therapy. Unfortunately, there is no way to know from administrative databases alone whether a patient is on monotherapy, and therefore some misclassification is inevitable without a full chart review; even then, there is room for misunderstanding and dosage errors on the patient’s part.

The relationship between adherence measures and diagnostic criteria depends on the accuracy of the physicians’ coding. Despite our efforts in the present study to create a cohort of newly diagnosed and treated patients, nearly one third had been treated before the index date. Extending the exclusion
period to 12 months without a claim for glaucoma or glaucoma therapy only improved this to 25%. This was a surprise and a concern, because the MPR was lower among those who had been treated previously (data not presented). Therefore, analyses of “newly treated” patient adherence may actually underestimate adherence for this subgroup.

In conclusion, research on the determinants of patients’ adherence to treatment requires reliable and valid measures of their medication patterns. The Glaucoma Adherence and Persistence Study used MPR and found that the median MPR for intraocular hypotensives in a database of almost 14,000 subjects was 0.64 ± 0.42. Using a more conventional survival curve or “gap” analysis, only 10% of patients had continuously refilled the index medication at 1 year. Clearly, many patients fail to use topical medications as prescribed. Large claims databases offer an opportunity to study adherence to medical therapy, but analysis requires methods that consider the many potential errors associated with the limited detail and imprecision of medical and pharmacy claims. We propose a methodological approach to these obstacles, both generally and when specific to topical glaucoma medications. We also highlight the limitations and potential sources of bias these approaches entail. The methodology presented herein provides an adherence metric that can be used as a foundation for analysis of the determinants of patient adherence, which can in turn help create novel, evidence-based approaches for helping patients and their physicians improve on the poor persistency and adherence documented in this report.

References

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933442/ on 06/24/2017