

Population-Based Persistency Rates for Topical Glaucoma Medications Measured with Pharmacy Claims Data

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Abstract

Background: Persistency with drug therapy reflects a number of factors, including patient tolerability of adverse events resulting from therapy and clinician satisfaction with the medication's effectiveness in reducing intraocular pressure.

Objective: This study assesses persistency with topical glaucoma medications administered as initial therapy by evaluating rates of discontinuation and change in therapy.

Methods: A retrospective cohort study was conducted using pharmacy claims data from 3 geographically diverse healthcare plans. Newly treated glaucoma patients younger than 65 years of age were selected based on an initial glaucoma medication fill during a 12-month period. Patients were followed for persistency, defined as discontinuation or change (switch or add-on) of initial glaucoma therapy; discontinuation of therapy was also evaluated as a separate end point.

Results: In all, 1330 patients (followed for 1126 person-years) met the eligibility criteria. Compared with latanoprost users, patients initiated on other topical monotherapies were more likely to discontinue or change therapy, and patients initiated on other topical monotherapies were more likely than latanoprost users to discontinue therapy.

Conclusion: Population-based data indicate that latanoprost offers superior persistency compared to agents from other popular classes of topical ocular hypotensives.

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Glaucoma is the second leading cause of blindness worldwide.¹ In the United States alone, more than 15 million persons are reported to have glaucoma.² The underlying mechanisms for development of the progressive,

irreversible optic nerve damage and visual field loss that characterize glaucoma have not been fully elucidated, but elevated intraocular pressure (IOP) is a major risk factor for development of the disease.³ Although not all patients with glaucoma exhibit elevated IOP levels, considerable evidence indicates that IOP reduction impedes progression of visual field defects in patients with glaucoma.⁴⁻⁷ As a result, medical treatment focuses on instillation of topical ocular hypotensive eye drops on a daily basis in order to reduce IOP levels.³

Primary open-angle glaucoma, the most common form of glaucoma in the United States, requires lifelong treatment, creating a financial burden for healthcare payers.⁸⁻⁹ Consequently, payers carefully evaluate glaucoma treatment patterns and their associated costs as they develop budget impact analyses. Such analyses enable healthcare payers to examine the affordability of a therapy, which may be a higher priority than examining the value of a therapy when budgets are constrained.¹⁰

Previous studies analyzed the economic impact of glaucoma therapy by evaluating the acquisition cost per day for different glaucoma treatments.¹¹⁻¹³ As an outcome, however, acquisition cost per day fails to account for the total cost of glaucoma disease management or the clinical value (cost-effectiveness) that accrues when patients persist with their glaucoma management plan. Patient persistency with glaucoma medications is of clinical importance because discontinuation of therapy

remains an important barrier to effective disease management in the population-based setting. In addition, departures from first-line therapy lead to increased medical costs because treatment changes are associated with increased monitoring, more frequent consultations and testing, and, in some cases, surgery.¹⁴ Common reasons cited for discontinuing or switching therapies include medication-related side effects, decreasing therapeutic effectiveness over time, and inconvenient dosing patterns.¹⁵

The objective of the present retrospective cohort study, conducted in 3 healthcare populations, was to evaluate population-based glaucoma medication persistency rates for the 4 most popular classes of glaucoma therapy.

Patients and Methods

This retrospective, population-based cohort study utilized a subset of the administrative health insurance claims database for AdvancePCS. This subset covered approximately 1.6 million lives annually and included 3 healthcare plans representing 3 different geographic regions in the United States: a mixed model plan representing the North Central United States; an independent practice association (IPA) representing the West Coast; and an indemnity (fee-for-service) plan representing the East Coast.

The study population included patients younger than 65 years of age with prescription drug coverage through 1 of the 3 healthcare plans. Included were newly treated glaucoma patients who received a prescription for one of the following topical glaucoma medications as monotherapy between February 1, 1999 and February 29, 2000: betaxolol, levobunolol, timolol, dorzolamide, brinzolamide, latanoprost, or brimonidine. Newly treated glaucoma patients were defined as those who had not received a prescription for any glaucoma medication and had not had glaucoma surgery in the 6 months prior to their index (initial) glaucoma prescription. Patients were followed through February 28, 2001. Patients who did not have continuous enrollment in the health plan

throughout the study period, including the 6 months prior to the index glaucoma prescription date, were excluded.

Persistency was evaluated using 2 separate end points. The first was a combined end point that included 2 parameters: discontinuation of therapy, defined as a gap of at least 120 days since the most recent glaucoma medication fill of patients' index glaucoma therapy; and change in glaucoma therapy, defined as a switch to a different glaucoma therapy or an addition to the index glaucoma therapy within 120 days of the most recent glaucoma medication fill. This cut-off point was selected by using the largest bottle size, which contains enough medication for 60 days of therapy, and assuming a 50% adherence rate (60 days/50% = 120 days). The second end point was therapy discontinuation, which focused strictly on discontinuation of patients' index glaucoma therapy and excluded any change in therapy (switches/add-ons).

Survival analysis methods were used to evaluate when patients discontinued or changed therapy. For the combined discontinuation and change in therapy analysis, patients were followed until the first occurrence of one of the following events: discontinuation of index therapy; change of index therapy; or end of study (censored). For the therapy discontinuation analysis (excluding change in therapy), patients were followed until the first occurrence of one of the following events: discontinuation of index therapy; change in therapy (censored); or end of study (censored). Because all patients were required to have continuous enrollment throughout the study period, no subject was censored because of loss to follow-up. For each end point, 4 Kaplan-Meier survival curves are presented representing the 4 classes of glaucoma medication: β -blockers (betaxolol, timolol, and levobunolol), carbonic anhydrase inhibitors (CAIs) (dorzolamide and brinzolamide), prostaglandins (latanoprost), and the widely used sympathomimetic, brimonidine. These curves provide a visual comparison of survival rates across classes of glaucoma therapy.

Table 1. Baseline Patient Characteristics

	β -Blockers	Brimonidine	CAIs	Latanoprost
Sample size (total = 1330)	785	178	47	320
Age, n (%)				
≤ 35	50 (6.4)	7 (3.9)	4 (8.5)	22 (6.9)
36 to ≤ 45	107 (13.6)	20 (11.2)	3 (6.4)	37 (11.6)
46 to ≤ 55	264 (33.6)	58 (32.6)	17 (36.2)	92 (28.8)
56 to < 65	364 (46.4)	93 (52.2)	23 (48.9)	169 (52.8)
Mean age [SD]	51.9 [10.0]	53.2 [9.8]	51.4 [13.3]	52.7 [10.6]
Sex, n (%)				
Female	369 (47.0)	97 (54.5)	20 (42.6)	179 (55.9)
Geographic distribution (healthcare plan), n (%)				
North Central (mixed model)	454 (57.8)	76 (42.7)	20 (42.6)	156 (48.8)
West Coast (IPA)	128 (16.3)	23 (12.9)	5 (10.6)	64 (20.0)
East Coast (indemnity)	203 (25.9)	79 (44.4)	22 (46.8)	100 (31.3)
Concomitant diseases, n (%)				
Diabetes	101 (12.9)	30 (16.9)	7 (14.9)	46 (14.4)
Cardiovascular disease	63 (8.0)	14 (7.9)	6 (12.8)	31 (9.7)

CAIs=carbonic anhydrase inhibitors.
IPA=Independent Practice Association.

A Cox proportional hazards regression model estimated the relative persistency across the 4 glaucoma drug classes after adjusting for patients' baseline characteristics. The Cox model generates hazard rate ratios (RRs) and 95% confidence intervals (CIs), which estimate the relative rates of persistency (discontinuation/change of therapy or only discontinuation of therapy) for each drug class, compared to a reference class. Before creating these models, the proportional hazards assumption was satisfied (ie, ensuring that the RR remained constant over follow-up) by comparing $-\ln(-\ln)$ survival curves for the 4 drug classes. Adjustments were made for the following covariates: age, sex, type of healthcare plan (which simultaneously adjusted for geographic region in the United States and type of insurance), and concomitant diseases (including diabetes and cardiovascular disease).

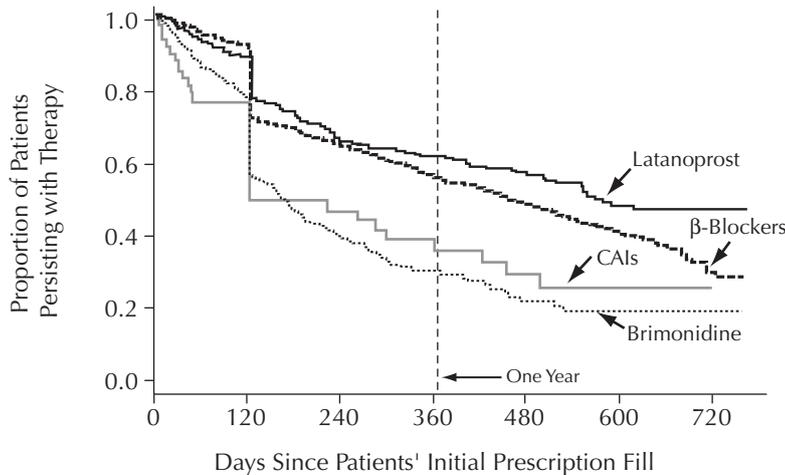
Results

In all, 1330 eligible patients were identified from the 3 healthcare plans during the study period. These 1330 patients

were followed for a total of 1126 person-years, a mean of 0.99 person-years. **Table 1** displays patient demographics for this study cohort, including age, sex, geographic distribution, and concomitant diseases, stratified by class of glaucoma therapy. β -blockers were the most frequently filled index prescriptions (59%), followed by latanoprost (24%), brimonidine (13%) and CAIs (4%). Most patients were between 46 and 65 years of age, and the majority were from the North Central region (53%) representing the mixed model plan, followed by the West Coast (30%) representing the IPA, and the East Coast (17%) representing the indemnity plan. Fourteen percent of patients had a history of diabetes, and 9% had a history of cardiovascular disease.

After 1 year of follow-up, the percentage of patients who discontinued or changed their index glaucoma therapy was lowest among latanoprost users (36%), followed by β -blocker users (41%), CAI users (57%), and brimonidine users (63%). Over the entire 2-year study period, 138 latanoprost users (43%), 413 β -blocker

Figure 1. Patient Persistency as Measured by Discontinuation of or Change in Initial Glaucoma Therapy (Unadjusted Kaplan-Meier Survival Curves)



The substantial decline in persistency at 120 days across therapies occurred because by definition patients could not discontinue their therapy before that time; declines before 120 days reflect changes in initial therapy. CAs = carbonic anhydrase inhibitors

users (53%), 30 CAI users (64%), and 123 brimonidine users (69%) discontinued or changed their glaucoma therapy. With regard to discontinuations only, 72 latanoprost users (23%), 289 β-blocker users (37%), 17 CAI users (36%), and 59 brimonidine users (33%) had discontinued their glaucoma therapy at the end of the follow-up period. The median length of persistency over 2 years was longest in patients treated with latanoprost (553 days), followed by those using β-blockers (150 days), brimonidine (159 days), and CAIs (120 days).

Kaplan-Meier curves for the combined discontinuation or change in glaucoma therapy end point are shown in **Figure 1**. Latanoprost users exhibited the greatest persistency by this end point, indicating that this group had the largest proportion of patients who continued their initial glaucoma therapy without discontinuing, switching, or adding on a new class of glaucoma therapy. Patients receiving β-blockers had the second highest proportion of patients persisting with their initial

therapy, followed by those treated with CAIs and brimonidine.

Figure 2 shows Kaplan-Meier curves for discontinuation in therapy (excluding switches/add-ons) for each of the 4 glaucoma drug classes. The curves are flat for the first 120 days because by definition patients could not discontinue their therapy during that time. Following this initial time period, the curves begin to separate as patients in each cohort experienced different rates of drug discontinuation. Discontinuation was lowest among patients using latanoprost, higher among those treated with β-blockers, and highest among patients receiving CAIs or brimonidine.

The RRs and 95% CIs from regression models for discontinuation and change of therapy using latanoprost as the reference drug category are shown in **Table 2**. (*Note:* $-\ln(-\ln)$ survivor curves confirmed no obvious violation of the proportional hazards assumption, suggesting a constant RR across the 4 drug classes over time for both outcomes.) Latanoprost users were less likely to discontinue or change therapy compared with patients treated with β-blockers (RR = 1.24; 95% CI, 1.02 to 1.50), CAIs (RR = 2.22; 95% CI, 1.49 to 3.29), or brimonidine (RR = 2.41; 95% CI, 1.89 to 3.07). Adjusting for age, sex, geographic region, and concomitant disease did not change these RRs substantially; the percent change in fully-adjusted versus unadjusted estimates were all less than 2%. For this reason, and to maintain compatibility between the numeric and graphical (Kaplan-Meier curves) representations, unadjusted estimates are reported.

Analyses of discontinuation of therapy alone demonstrated that latanoprost users were less likely to discontinue therapy than patients receiving β-blockers (RR = 1.63; 95% CI, 1.26 to 2.11), CAIs (RR = 2.37; 95% CI, 1.40 to 4.03), or brimonidine (RR = 2.26; 95% CI, 1.60 to 3.19). Again, little evidence of confounding by covariates was seen, given the very small percent changes in estimates after adjustment; thus, unadjusted estimates are reported.

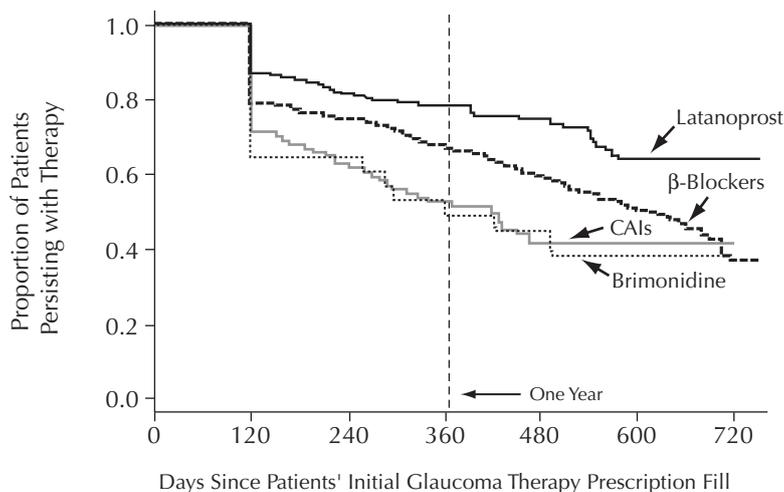
Discussion

Persistency with drug therapy reflects

patient satisfaction with tolerability of adverse events resulting from therapy and clinician satisfaction with the medication's effectiveness in reducing IOP. The present study assessed persistency with patients' initial glaucoma therapy by evaluating rates of discontinuation and change of therapy using population-based pharmacy claims data. Four classes of ocular hypotensives were compared across 3 populations of patients who started therapy between February 1999 and February 2000. Overall, newly treated glaucoma patients initiated on latanoprost were more persistent than patients initiated on other classes of monotherapy. For the 2 separate persistency end points, latanoprost users experienced the lowest rate of combined discontinuation/change (switch/add-on) of therapy and the lowest rate of therapy discontinuation (excluding change in therapy). Greater persistency may result in a favorable budget impact by reducing the frequency of ophthalmology visits and other glaucoma management costs attributable to discontinuation/changes in therapy.¹⁴

Results of this study are consistent with those of a retrospective cohort study of 264 newly diagnosed glaucoma patients conducted in the United States. In that research, 50% of patients initiated on β -blocker monotherapy remained persistent after 2 years.⁸ This rate was only slightly higher than the 47% 2-year persistency

Figure 2. Patient Persistency as Measured by Discontinuation of Initial Glaucoma Therapy (Unadjusted Kaplan-Meier Survival Curves)



The curves are flat for the first 120 days because by definition patients could not discontinue their therapy during that time. CAIs=carbonic anhydrase inhibitors.

rate found for β -blockers in the present study. Persistency rates in patients treated with latanoprost, CAIs, or brimonidine have not previously been reported.

Given the relationship between reduced IOP levels and delayed disease progression,⁴⁻⁷ IOP often is used as a surrogate marker of visual function outcome. Randomized clinical trials report greater

Table 2. Relative Discontinuation of or Change in Glaucoma Therapy by Initial Glaucoma Therapy

Initial Drug Choice	Therapy Discontinuation or Change (Switch/Add-on)		Therapy Discontinuation (Excluding Change of Therapy)	
	RR	95% CI*	RR	95% CI*
Latanoprost†	1.00	—	1.00	—
β -blockers	1.24	1.02-1.50	1.63	1.26-2.11
CAIs	2.22	1.49-3.29	2.37	1.40-4.03
Brimonidine	2.41	1.89-3.07	2.26	1.60-3.19

*Estimated by unadjusted hazard rate ratios (RRs) and 95% confidence intervals (CIs) from Cox regression models.

†Reference group.

CAIs=carbonic anhydrase inhibitors.

IOP reduction among patients treated with latanoprost compared with those treated with either the β -blocker, timolol¹⁶⁻¹⁸ or the CAI, dorzolamide.¹⁹ Two recently reported multicenter, randomized, double-masked trials found latanoprost to be significantly more effective in reducing IOP than brimonidine,²⁰⁻²¹ although a smaller double-masked, parallel-design trial found the 2 drugs provided comparable IOP lowering at peak effect.²² In general, rates of serious ocular adverse events have been reported to be low for all classes of drugs included in this study while the systemic safety profile of latanoprost has been ranked highest.²³

In studying drug persistency, using pharmacy claims data from an observational cohort study population has benefits as well as limitations compared to using data from a randomized clinical trial. Benefits of pharmacy claims databases include that they are population-based, representing large populations typical of routine practice, and they include patients who would most likely be excluded by trial eligibility criteria. Moreover, the larger size of these cohort studies improves precision, essential for studying the rare adverse events that contribute to discontinuation or changes in drug therapies. Analyses are relatively inexpensive because data are already collected and computerized for administrative purposes.

Pharmacy claims data also have important limitations. First, such information does not allow direct observation of therapy discontinuation; the event is assumed to have occurred when no refill is recorded. Second, claims data do not include information about daily adherence to a drug. Rates of and reasons for noncompliance with ocular hypotensives are well documented.^{15,24-26} It is also the case, however, that refill compliance is a useful source of compliance information when it is not possible to directly measure patient adherence to medication regimens.²⁷ Third, the possibility that some patients supplement their regimens with samples obtained from a physician is not taken into account. Fourth, reasons for discontinuation or change of therapy are not identifiable and await

prospective, population-based studies. Finally, pharmacy claims data lack potentially important information pertaining to baseline characteristics of patients, such as IOP, earlier episodes of topical therapy, and duration and severity of glaucoma. These factors may not only predict drug persistency but also which class of treatment a patient is prescribed. In particular, severity of illness will act as a confounder if it predicts which drug a patient is prescribed and if it is associated with a higher rate of discontinuation or change in therapy. For example, latanoprost, which currently is not indicated as first-line therapy, may be preferentially prescribed to patients with higher baseline IOP levels or long-standing glaucoma; such potentially refractory patients may be more likely to have another topical hypotensive added to their regimen. In contrast, β -blockers are indicated as first-line therapy and may be prescribed to patients with a more benign baseline profile.

Persistency with medication is important for effective management of disease. Clinical trials show that ocular hypotensive medications reduce IOP, thus slowing progression of visual impairment.⁴ Lack of persistency with topical glaucoma medication can lead to increased healthcare utilization and costs associated with more frequent visits to healthcare providers and the need for more aggressive and costly treatment.¹⁴ The present observational cohort study has the advantages of being population-based, of including patients typical of routine practice, and of accounting for aspects of disease management that simpler studies of the acquisition costs of glaucoma therapies cannot. The results indicate that patients who receive latanoprost as their initial glaucoma therapy exhibit greater persistency compared with those treated with other antihypotensive monotherapies.

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