Discontinuation Rates of Topical Glaucoma Medications in a Managed Care Population

Fadia T. Shaya, PhD, MPH; C. Daniel Mullins, PhD; Winston Wong, PharmD; and Jeannie Cho, PharmD

Abstract

Background: Rates of medication discontinuation reflect factors including effectiveness, tolerability, cost, and dosing frequency. Discontinuation data can be useful to physicians and health plan managers as they compare various glaucoma medications.

Objective: To compare rates of discontinuation of therapy in patients initially prescribed monotherapy with a topical glaucoma medication.

Methods: Members of a managed care plan who filled at least 1 prescription for latanoprost, timolol, or brimonidine during a 30-month period were eligible to participate in this study. Prescription refill records for all glaucoma agents used in the plan were extracted for the study period. Rates of discontinuation of initial glaucoma therapy were compared using Cox regression methods; Kaplan-Meier survival curves were generated.

Results: A total of 72,744 prescriptions were eligible, of which 48,491 were for study drugs. Latanoprost was the most frequently dispensed therapy (accounting for 49.7% of study drugs), followed by timolol (30.6%), and brimonidine (19.6%). After inclusion and exclusion criteria were applied, 2283 patients were included in analyses. Latanoprost-treated patients were significantly less likely to discontinue medication than were those treated with timolol or brimonidine. Kaplan-Meier survival curves confirmed that latanoprost-treated patients exhibited the greatest persistency with therapy.

Conclusion: In this managed care setting, rates of discontinuation in patients initially treated with latanoprost were lower than those of patients receiving comparator drugs.

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Glaucoma, a term that represents a group of diseases characterized by progressive optic neuropathy, is estimated to account for 15% of the burden of blindness worldwide.[1] Primary open-angle glaucoma (POAG), the most common form of glaucoma in Western developed countries, affects approximately 15 million Americans, 150,000 of whom have bilateral blindness from the disease.[2] Unfortunately, many who are at high risk for the condition, including those who are older than 60 years of age, African Americans, and individuals with a family history of glaucoma,[2] are unaware of the importance of early detection and do not seek medical care.[3]

POAG typically is characterized by mid-peripheral visual field loss and excavation of the optic disk.[2,4] Although the causes of POAG are not clear, elevated intraocular pressure (IOP) is a major risk factor for the disease[4] and results from the impaired outflow of aqueous humor.[5] Current treatments focus on lowering IOP levels because such decreases have been associated with reduced progression of visual field defects.[6] Although new glaucoma therapies that promote nerve protection and neuroregeneration are under development,[7,8] treatment with topical ocular hypotensives, which improves aqueous humor drainage and/or reduces aqueous humor production,[5] remains the therapeutic mainstay in newly diagnosed patients. In patients for whom pharmacologic therapies are ineffective, laser trabeculoplasty or surgical trabeculectomy may be performed to improve the flow of aqueous humor.[2]

β-Blockers became the leading pharmacologic treatment for glaucoma soon after they were introduced in 1978 because of their effectiveness, local tolerability, and relative convenience of dosing (twice daily).[9] Systemic absorption following topical administration of β-blockers may lead

to blocking of β_1-adrenoceptors of the heart or β_2-adrenoceptors in the bronchioles, however, resulting in bradycardia, arrhythmia, congestive heart failure, or bronchospasm.[4] If monotherapy with a β-blocker is contraindicated, is associated with unacceptable side effects, or does not induce a useful reduction in IOP within 1 month, an alternative monotherapy should be tried. The topical prostaglandins (such as latanoprost), carbonic anhydrase inhibitors (including dorzolamide and brinzolamide), or α_2-adrenergic agonists (such as brimonidine) currently represent the best pharmacotherapeutic options.[9]

No pharmacologic therapy can succeed unless patients adhere to the treatment regimen. Lack of adherence takes many forms, including not having a prescription filled or refilled, taking the agent at the incorrect dose or at the wrong time, or not completing the course of therapy. Poor medication adherence with glaucoma medications often is under-appreciated by physicians and difficult to detect in clinical practice.[10] Lapses have been attributed by patients to a lack of clinical effectiveness, adverse side effects, or inconvenient dosing regimens.[11]

Medication persistency, that is continuing a given therapeutic regimen over time, is one form of adherence. With regard to topical glaucoma medications, persistency may be considered a surrogate marker for the physician's satisfaction with effectiveness (IOP control) and the patient's satisfaction with tolerability. Although changes in initial glaucoma therapy have been associated with increases in healthcare resource utilization, earlier surgical interventions, and higher costs, physicians usually do not have systematic or reliable methods to identify persistency rates in their clinical practices.[12] The goal of the present study was to compare rates of discontinuation of therapy in patients initially prescribed monotherapy with a topical glaucoma medication.

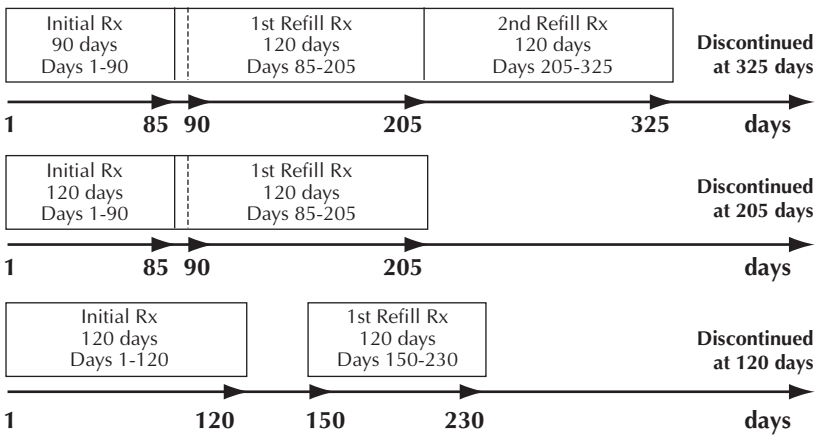
Methods

A retrospective analysis of information in the prescribing database for CareFirst BlueCross BlueShield members was conducted. Information was retrieved from the database at AdvancePCS, the prescription benefit manager, made available in ApotheQuery™ software. Included were all members of the Maryland CareFirst BlueCross BlueShield managed care plan, either indemnity or FreeState, who filled at least 1 prescription for a glaucoma therapy between January 1, 1999, and July 1, 2001. Patients were excluded if they were not continuously enrolled (had an enrollment gap >1 day) in CareFirst BlueCross BlueShield or were prescribed any glaucoma drug in the 180 days prior to their initial dispensing date. In addition, patients younger than 20 or older than 64 years of age were excluded. Patient race was not included in the database and therefore was not analyzed.

Prescription refill records for all glaucoma agents used in the plan were extracted for the 30-month study period. The initial dispensing date of the first study drug was recorded for each patient, and a rolling basis timeline was observed at 120-day intervals. If a refill of the same drug occurred within 120 days of the initial dispensing date, this new date was recorded as the last dispensing date. If another same drug refill occurred within 120 days of that last dispensinig date, then a new dispensing date was recorded. If a prescription for a different ocular hypotensive was filled during the 120-day period, the patient was excluded from the analysis. The process was repeated until no refill of the same drug was obtained by the patient, in which case a discontinuation was recorded.

Figure 1 illustrates 3 different refill scenarios. In the first instance, an overlap occurs between the initial fill and the first refill and also between the first and second refills; the time to discontinuation of therapy, or the persistency period, is calculated as 325 days. In the second instance an overlap occurs between the initial fill and the first refill, making the total persistency period 205 days. The last example illustrates a gap of 30 days between the initial fill and the first refill; the persistency period is the initial 120 days only.

Figure 1. Timelines Illustrating Discontinuation of Therapy Model



Rx=prescription.

This study was conducted from the perspective of the payer, and the unit of analysis was the patient. As a first step, an exploratory analysis using general means was performed to identify gross patterns of use and to describe the patient population profile. Chi-square tests were used to evaluate the significance in the differences in proportions of patients in the various treatment groups with respect to age and sex. Cox regression models (unadjusted and adjusted by age and sex) were developed to compare hazard rate ratios (RRs) of discontinuation among the study drug cohorts. Kaplan-Meier survival curves were generated to quantify the time to drug discontinuation and to illustrate time trends in patients treated initially with comparator drugs versus latanoprost. The survival analysis was performed using the program SAS V8, while preliminary analyses were performed in the programs Excel and Access.

Results

The query of the prescribing database for all glaucoma therapies used in the plan during the study period yielded a total of 72,744 prescriptions (**Table 1**), representing 14 different drugs. The most frequently dispensed therapy was latanoprost (accounting for 33.2% of all prescriptions), followed by timolol (20.4%), and brimonidine (13.1%). The drugs least frequently dispensed were bimatoprost (0.1%), brinzolamide (1.6%), echothiophate iodide (0.2%), travoprost (0%), and unoprostone isopropyl (0.1%). Further analyses included only the 3 most frequently prescribed

Table 1. Dispensing Frequency of Ocular Hypotensives

Generic Name	Count	Percent of All Ocular Hypotensives
Betaxolol hydrochloride	3724	5.1
Bimatoprost	79	0.1
Brimonidine tartrate	9510	13.1
Brinzolamide	1186	1.6
Carteolol hydrochloride	3005	4.1
Dorzolamide hydrochloride	3195	4.4
Echothiophate iodide	142	0.2
Latanoprost	24,123	33.2
Levobunolol hydrochloride	2969	4.1
Pilocarpine hydrochloride	3467	4.8
Timolol maleate	14,858	20.4
Timolol/dorzolamide	6376	8.8
Travoprost	44	0.0
Unoprostone isopropyl	66	0.1
Total	**72,744**	**100.0**

drugs: latanoprost, timolol, and brimonidine. Including only those 48,491 prescriptions, latanoprost was most frequently dispensed (49.7% of all prescriptions), followed by timolol (30.6%) and brimonidine (19.6%). After inclusion and exclusion criteria were applied and patients rather than prescriptions were counted, 2283 patients were included in final analyses; 858 were treated initially with latanoprost, 939 with timolol, and 486 with brimonidine (**Table 2**). Women were somewhat more numerous than men in all treatment groups, representing 53.6% of the sample overall. Nearly two thirds of patients were 50 through 64 years of age. Differences among therapeutic groups with respect to age and sex distributions were not statistically significant.

Cox regression models both unadjusted and adjusted for age and sex are shown in **Table 3**. Latanoprost-treated patients were significantly less likely to discontinue medication than were those treated with timolol (RR = 1.36,; 95% confidence interval [CI], 1.28 to 1.43) or brimonidine (RR = 1.54; 95% CI, 1.44 to 1.63) ($P < .0001$ for each comparison). Overall, patients treated with timolol or brimonidine were approximately 36% and 54%, respectively, more likely to discontinue medications during the study period than were patients treated initially with latanoprost. Results of analyses adjusted for age and sex were nearly identical (Table 3). **Figure 2** shows the Kaplan-Meier curve of time to discontinuation for latanoprost, brimonidine, and timolol. Latanoprost-treated patients exhibited the greatest persistency with therapy.

Discussion

From the standpoint of managed care plans, glaucoma therapies are neither the highest volume nor highest dollar-value medications prescribed. Given that glaucoma is a chronic disease and a major cause of vision loss, however, persistency with pharmacologic regimens that can reduce IOP levels and delay progression of visual field defects should enhance clinical, humanistic, and economic outcomes. Thus, plans in which large proportions of glaucoma patients are treated with ocular hypotensives that have low discontinuation rates may expect long-term reductions in follow-up visits, testing, counseling, and surgery, all of which are services that negatively affect the quality of life of patients and increase the cost of care.

Results of the present study show that patients treated initially with latanoprost are less likely to discontinue therapy than those who are treated with timolol or brimonidine, a result confirmed in analyses adjusted for age and sex. Interestingly, latanoprost also was the most commonly prescribed drug in the plan, accounting for 33.2% of prescriptions overall and for 49.7% of prescriptions for the 3 most commonly dispensed drugs. Although latanoprost

Table 2. Patient Population by Sex and Age Group: n (%)

	Sex*		Age Group† (years)			
	Female (%)	**Male (%)**	**20-34 (%)**	**35-49 (%)**	**50-64 (%)**	**Total (%)**
Latanoprost	444 (51.8)	414 (48.2)	49 (5.7)	242 (28.2)	567 (66.1)	858 (37.6)
Timolol	510 (54.3)	429 (45.7)	73 (7.8)	277 (29.5)	589 (62.7)	939 (41.1)
Brimonidine	269 (55.4)	217 (44.6)	28 (5.8)	133 (27.4)	325 (66.9)	486 (21.3)
Total	1223 (53.6)	1060 (46.4)	150 (6.6)	652 (28.6)	1481 (64.8)	2283 (100.0)

*Chi-square = 1.97, $df = 2$, $P = 0.37$.
†Chi-square = 5.25, $df = 4$, $P = 0.26$.

belongs to a relatively new class of drugs, the topical prostaglandins, prescribers have adopted it rapidly in this managed care plan. The level of acceptance of a new therapy depends on many elements, including its effectiveness, side-effect profile, dosing regimen, and ease of administration. Previous research has demonstrated the superior efficacy and tolerability of latanoprost,[13-17] and the drug is convenient to use, requiring instillation just once daily. To the extent that the high prescribing and low discontinuation rates of latanoprost reflect these factors, patients, physicians, and payers will benefit.

Future research might focus on identifying ways for clinicians to more effectively individualize antiglaucoma therapy and on training patients in disease management techniques. With regard to individualizing therapy, research concerning potential differences by race in discontinuation patterns would be worthwhile given existing evidence that open-angle glaucoma tends to develop earlier[18] and progress more rapidly[19-20] in African Americans than in Caucasians and that responses to surgical therapy differ across racial groups.[20] Results of a study by Eckman et al[21] are instructive with regard to the issue of patient education. These authors trained patients with schizophrenia in methods of obtaining information about medications, administering medications and evaluating their benefits, identifying medication side effects, and negotiating with healthcare providers; over 3 months of follow-up, patients showed enhanced knowledge about medications, heightened skill utilization, and improved med-ication adherence. The impact of such interventions on persistency could usefully be tested in glaucoma patients.

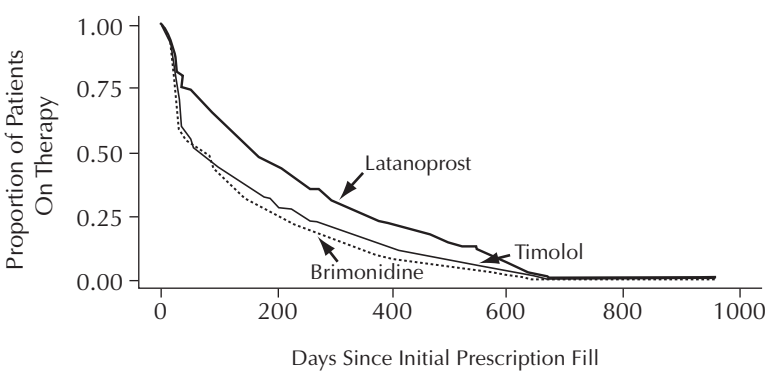
This study has both strengths and limitations. The main advantage is the large sample size that provided sufficient power to test for differences in rates of discontinuation among the ocular hypotensives most commonly dispensed in the managed care plan. In contrast to a cross-sectional, pretest/posttest design, the present retrospective study observed discontinuations that had already occurred, thereby eliminating observer or subject bias. The survival analysis method used all prescription refill data for each patient, providing a profile of discontinuations across time. Internal validity was enhanced by the inclusion only of patients who were continuously enrolled in the plan and who were enrolled for the 6 months prior to the study initiation date; thus, patients who did not refill prescriptions simply because they were no longer plan members were not evaluated. In addition, only patients ages 20 through 64 were includ-

Table 3. Relative Discontinuation in Glaucoma Therapy*

Variable	RR	95% CI	*P* Value
Unadjusted model			
Latanoprost†	1.00	—	—
Timolol	1.36	1.28-1.43	<.0001
Brimonidine	1.54	1.44-1.63	<.0001
Model adjusted for sex and age			
Latanoprost†	1.00	—	—
Timolol	1.34	1.27-1.41	<.0001
Brimonidine	1.54	1.45-1.62	<.0001

*Hazard rate ratios (RR) and 95% confidence intervals (CI) from Cox regression models.
†Reference group.

Figure 2. Time to Discontinuation of Brimonidine, Latanoprost, and Timolol (Adjusted Kaplan-Meier Curves)



ed, thereby excluding confounders for which the study design could not properly control such as large numbers of comorbidities and the fact that complete prescription claims information for patients 65 and older may not be available in the database of any single managed care plan.

Analyses based on claims data carry inherent limitations. First, it can only be assumed that prescriptions submitted for reimbursement reflect all prescriptions filled. Second, it is not known whether patients actually take the drugs for which they fill a prescription. Although results of research suggest that noncompliance with ocular hypotensive therapies is common,[11,22-24] refill compliance measures have been found to be useful when direct measures of patient compliance are not available.[25] Third, some patients may supplement their regimens with samples obtained from the physician. Fourth, external validity might be threatened by hidden treatments received by certain drug cohorts and not others. For instance, a given drug might be coupled with more thorough pharmaceutical care, counseling, and follow-up, thereby creating a better adherence profile. However, no evidence was seen that such a situation occurred in the case of topical glaucoma medications and in the context of the managed care plan.

Finally, although the generalizability of results may be limited by the fact that only patients enrolled in a managed care plan were included, other patient characteristics were generally similar to those found more broadly. Thus, the present sample included a somewhat larger proportion of females than males, a finding consistent with reports that women utilize health services at a higher rate than men.[26-27] In addition, the age distribution in the present research is consistent with the known epidemiology of glaucoma; nearly two thirds of patients receiving therapy were 50 to 64 years of age, while fewer than 10% of patients were younger than 35 years of age.[2-3]

In conclusion, while the search for new, effective therapies must continue, efforts focused on decreasing medication discontinuation may have a greater overall impact on health than the discovery of any single new agent.[28-29] Results of the present study of ocular hypotensive use in a managed care population demonstrate that the rate of discontinuation of therapy in patients initially treated with latanoprost was lower than such rates in patients receiving comparator drugs. Physicians and health plan managers can use such information as they decide which glaucoma medications to prescribe to individual patients and as they evaluate the affordability of various therapies.

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