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Patient persistency with pharmacotherapy in the management of glaucoma

G. REARDON[1], G.F. SCHWARTZ[2], E. MOZAFFARI[3]

[1]Informagenics, LLC, Worthington, OH
[2]Glaucoma Consultants, Greater Baltimore Medical Center; Wilmer Eye Institute, Johns Hopkins University; University of Maryland, Baltimore, MD
[3]Pharmacia Corporation, Peapack, NJ - USA

PURPOSE. *To evaluate persistency with monotherapy in the treatment of glaucoma in patients new to pharmacological management.*
METHODS. *This population-based, retrospective cohort study, using managed care administrative claims data, included patients who were 20 years of age and older and who initiated monotherapy with betaxolol, brimonidine, dorzolamide, latanoprost, or timolol between May 1999 and January 2001. Follow-up continued through January 31, 2001, and prescription refill records for all ocular hypotensive medications were extracted for the full 21-month study period. The primary outcome measures were discontinuation and change (switching/adding on) of the index ocular hypotensive medication. Rates of discontinuation and discontinuation/change were compared using Cox regression methods; survival curves were generated.*
RESULTS. *In all, 14,539 patients were prescribed any ocular hypotensive drug during the study period, and 2850 patients met all inclusion criteria. Patients treated with betaxolol, brimonidine, dorzolamide, or timolol were significantly ($p<0.05$) more likely to discontinue and to discontinue/change the index therapy than were those treated with latanoprost. Results were confirmed in analyses adjusted for age and sex.*
CONCLUSIONS. *Patients initially treated with latanoprost monotherapy are more persistent than those who begin treatment with beta-blockers, brimonidine, or the carbonic anhydrase inhibitor dorzolamide. Greater persistency with an initial ocular hypotensive therapy may improve health outcomes and reduce long-term costs to patients and health plans by limiting the increased resource use associated with discontinuations or changes in therapy.*
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KEY WORDS. *Glaucoma, Health economics, Latanoprost, Ocular hypotensive therapy*

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INTRODUCTION

Glaucoma is a group of eye diseases that can gradually cause blindness due to progressive optic neuropathy. Currently, glaucoma management focuses on lowering intraocular pressure (IOP) levels using either ocular hypotensive medications or surgery (1) because such reductions have been associated with diminished disease progression (2-5). Topical beta-blockers, such as timolol and betaxolol, were introduced in 1978 and quickly became the leading pharmacological treatments for glaucoma (6). Their effectiveness, local

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tolerability, and relative convenience are offset, however, by the fact that systemic absorption of these topical drugs may result in arrhythmia, bradycardia, exacerbation of congestive heart failure symptoms, or bronchospasm (7). At present, the favored pharmacotherapeutic options are the topical prostaglandin analogues (including latanoprost), the α_2-adrenergic agonists (such as brimonidine), and the carbonic anhydrase inhibitors (including dorzolamide) (6). Drugs in each of these classes have been shown to lower IOP levels at least as effectively as timolol (8-11).

In order for a pharmacological therapy to be effective, patients must fill their prescriptions over time (persistency) and take the medications as directed (compliance). Patients have attributed poor compliance with ocular hypotensive regimens to a therapy's lack of effectiveness, adverse side effects, or inconvenient dosing (12). For chronic pharmacotherapy, compliance cannot be achieved without persistency because the patient must continue to refill prescriptions prior to consuming them. Persistency with ocular hypotensives reflects both the physician's satisfaction with IOP control and the patient's satisfaction with medication tolerability (13). Dissatisfaction by either party may lead to adding another medication to the therapeutic regimen, switching to another medication, or discontinuing ocular hypotensive therapy completely. These outcomes can have serious consequences as therapy discontinuation limits physicians' efforts to control patients' IOP levels while changes in therapy may reflect inadequacies with regard to effectiveness or tolerability and can increase health care costs.

Recent research suggests that persistency with ocular hypotensives varies across medication types and that patients treated with latanoprost are more persistent than those receiving other therapies (14-16). The purpose of the present research was to further evaluate persistency with monotherapy in the treatment of glaucoma in patients new to pharmacological management.

PATIENTS AND METHODS

This population-based, retrospective cohort study used claim records from a large New England (United States) insurer. Included were patients 20 years of age and older who initiated monotherapy between May 1999 and January 2001 with one of the following ocular hypotensive medications: betaxolol, brimonidine, dorzolamide, latanoprost, or timolol. Patients were excluded if they were not continuously enrolled in the insurance plan or were prescribed any ocular hypotensive medication in the 180 days prior to the initial dispensing date. Follow-up continued through January 31, 2001, and prescription refill records for all ocular hypotensive medications were extracted for the full 21-month study period.

Drug persistency was calculated as the time period from the initial topical ocular hypotensive (index) medication dispensing date to the time of index medication discontinuation or to the time of change in the index medication (switch or add). Patients were identified as discontinuing therapy if they had no further ocular hypotensive medication refills 120 days (if dispensed 1 bottle) or 180 days (if dispensed >1 bottle) after the previous fill date; days of therapy on the index drug before discontinuation were calculated as the discontinuation date minus the initial dispensing date. These time frames were based on analyses of time between refills for 16 selected ocular hypotensive agents used by 48,978 patients in a United States managed care administrative database between January 1996 and March 2002 (Informagenics, LLC, unpublished data, October 2002). The mean number of days between refills across products ranged from 34 to 86 days for single-bottle fills, and the 120-day interval between refills used here allowed for some variation in prescription dosing and for noncompliance (eg, skipping doses or every-other-day usage). Patients were identified as changing therapy if they switched or added a topical ocular hypotensive medication other than the index agent; days of therapy on the index drug before changing therapy were calculated as the date of therapy change minus the initial dispensing date. Data were censored if patients either disenrolled from the insurance plan or reached the end of the study period prior to therapy discontinuation or change.

Chi-square tests were used to assess differences in proportions of patients in the various treatment groups with respect to age, sex, and initial diagnosis. Cox regression models (unadjusted and adjusted by age and sex) were calculated to compare hazard rate ratios (RRs) of discontinuation or discontinuation/change across treatment groups, with latanoprost as the comparator. Plots of survival functions were constructed from the Cox

model results to provide visual comparisons among treatment groups of the likelihood of remaining persistent with ocular hypotensive therapy over time. All statistical analyses were performed using SPSS Version 11.0 (Chicago, IL, USA).

RESULTS

In all, 14,539 patients were prescribed any ocular hypotensive drug during the study period, and 2850 patients met all additional inclusion criteria and were included in the analysis (Tab. I). In the final cohort, the most frequently dispensed drug was timolol (prescribed to 49.4% of patients), followed by latanoprost (24.0%), brimonidine (18.4%), betaxolol (5.7%), and dorzolamide (2.5%) (Tab. II). Men and women were represented approximately equally in the sample, about three quarters of patients were 50 years of age or older, and nearly half were diagnosed with primary open-angle glaucoma.

A total of 1107/2850 patients (38.8%) discontinued the index drug within 21 months of the index prescription date. Cox regression model statistics for discontinuation, both unadjusted and adjusted for sex and age, are shown in Table III. In both models, patients treated with timolol, brimonidine, betaxolol, or dorzolamide were significantly more likely to discontinue the index therapy than were those treated with latanoprost. Figure 1 shows survival plots in the adjusted model for discontinuation for all study drugs. Latanoprost-treated patients demonstrated the greatest persistency with therapy over time.

Overall, 1635/2850 patients (57.4%) discontinued or changed therapy within 21 months of the index prescription date. Table IV presents the unadjusted and adjusted relative risks of either discontinuing or changing therapy. Compared to latanoprost, patients treated with timolol, brimonidine, betaxolol, or dorzolamide were significantly more likely to discontinue or change therapy. Figure 2 includes survival plots for discontinuing or changing therapy for all study drugs based on the adjusted model.

DISCUSSION

Results of several studies have demonstrated that IOP reduction slows the progression of glaucomatous optic neuropathy (2-5). Although patient compliance with medication regimens is required for such IOP reductions to occur, nearly one quarter of open-angle glaucoma patients have been found to be noncompliant with their topical ocular hypotensive therapy during the first year of treatment (17). It seems likely that selection of an agent that effectively lowers IOP

TABLE I - APPLICATION OF EXCLUSION CRITERIA TO PATIENT POPULATION

Exclusion criteria	Number excluded	Number included
Initial population of patients prescribed an ocular hypotensive drug between May 1, 1999 and January 31, 2001	—	14.539
Enrollment data missing or patient had incomplete medical care utilization data from insurance claims	1800	12.739
Patient did not have continuous drug benefit enrollment for 180 days before index prescription date	3670	9069
Patient <20 years of age 180 days before index prescription date	46	9023
Patient did not receive index prescription for betaxolol, brimonidine, dorzolamide, latanoprost, or timolol monotherapy	1518	7505
Patient received any ocular hypotensive medication within 180 days before index prescription date, ie, was not new to ocular hypotensive drug therapy	3859	3646
Patient had ocular trauma or glaucoma surgery within 180 days before index prescription date	796	2850

TABLE II - PATIENT DEMOGRAPHICS, n (%)

	Latanoprost	Timolol	Brimonidine	Betaxolol	Dorzolamide	Total
Patient	683 (24.0)	1408 (49.4)	523 (18.4)	164 (5.7)	72 (2.5)	2850 (100.0)
Age (yrs)						
20 to 34	13 (1.9)	42 (3.0)	12 (2.3)	3 (1.8)	2 (2.8)	72 (2.5)
35 to 49	124 (18.2)	290 (20.6)	91 (17.4)	23 (14.0)	9 (12.5)	537 (18.8)
50 to 64	289 (42.3)	603 (42.8)	235 (44.9)	68 (41.5)	23 (31.9)	1218 (42.7)
>64	257 (37.6)	473 (33.6)	185 (35.4)	70 (42.7)	38 (52.8)	1023 (35.9)
Male	328 (48.0)	718 (51.0)	238 (45.5)	84 (51.2)	33 (45.8)	1401 (49.2)
Type of glaucoma						
Open angle	339 (49.6)	629 (44.7)	250 (47.8)	62 (37.8)	32 (44.4)	1312 (46.0)
Suspected*	125 (18.3)	200 (14.2)	91 (17.4)	22 (13.4)	6 (8.3)	444 (15.6)
Other	59 (8.6)	136 (9.7)	49 (9.4)	16 (9.8)	1 (1.4)	261 (9.2)
Not documented	160 (23.4)	443 (31.5)	133 (25.4)	64 (39.0)	33 (45.8)	833 (29.2)
Frequency of glaucoma visits in the 180 days prior to date of index medication						
0	226 (33.1)	547 (38.8)	171 (32.7)	67 (40.8)	34 (47.2)	1045 (36.7)
1	220 (32.2)	470 (33.4)	153 (29.3)	59 (36.0)	20 (27.8)	922 (32.3)
>1	237 (34.7)	391 (27.8)	199 (38.0)	38 (23.2)	18 (25.0)	883 (31.0)

*Includes suspected open-angle glaucoma and ocular hypertension

TABLE III - RELATIVE RISK OF *DISCONTINUATION* IN GLAUCOMA THERAPY*

Variable	RR	95% CI	p value
Unadjusted model			
Latanoprost†	1.00	-	-
Timolol	1.78	1.51, 2.10	<0.001
Brimonidine	1.68	1.36, 2.08	<0.001
Betaxolol	2.10	1.63, 2.70	<0.001
Dorzolamide	1.62	1.09, 2.40	0.016
Model adjusted for sex and age			
Latanoprost†	1.00	-	-
Timolol	1.77	1.50, 2.09	<0.001
Brimonidine	1.67	1.35, 2.06	<0.001
Betaxolol	2.14	1.66, 2.75	<0.001
Dorzolamide	1.71	1.15, 2.54	0.008

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

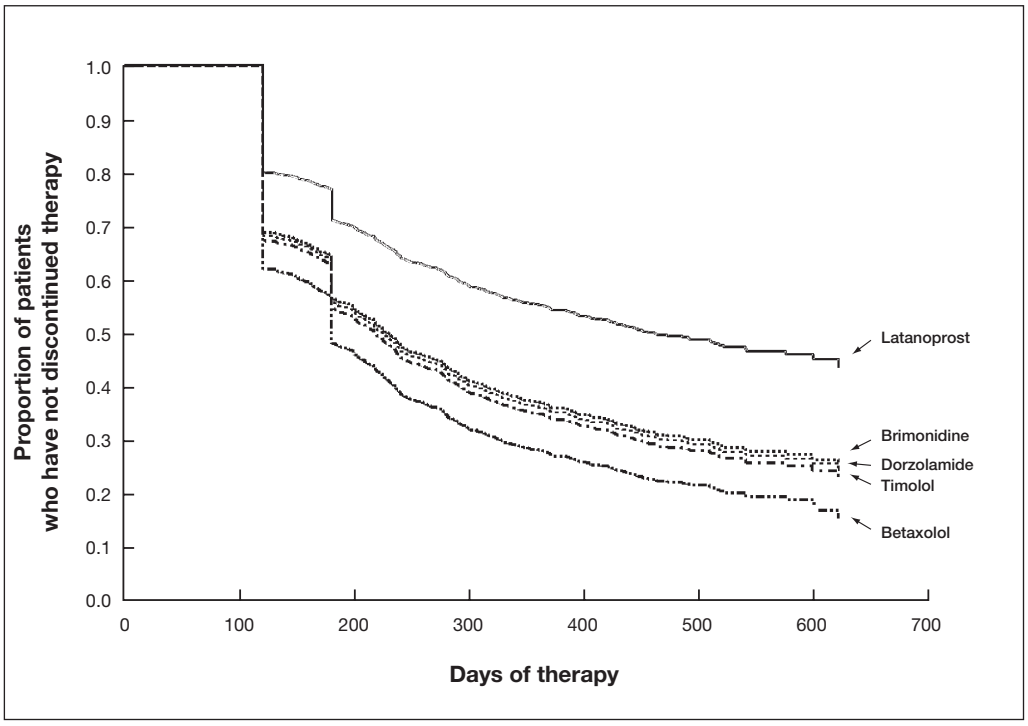

Fig. 1 - *Plot of survival function for time to discontinuation; adjusted Cox regression model.*

TABLE IV - RELATIVE RISK OF *DISCONTINUATION OR CHANGE* IN GLAUCOMA THERAPY*

Variable	RR	95% CI	p-value
Unadjusted model			
Latanoprost†	1.00	-	-
Timolol	1.36	1.19, 1.56	<0.001
Brimonidine	1.88	1.61, 2.20	<0.001
Betaxolol	1.58	1.27, 1.95	<0.001
Dorzolamide	1.49	1.09, 2.03	0.012
Model adjusted for sex and age			
Latanoprost†	1.00	-	-
Timolol	1.36	1.19, 1.55	<0.001
Brimonidine	1.87	1.60, 2.19	<0.001
Betaxolol	1.60	1.29, 1.98	<0.001
Dorzolamide	1.53	1.12, 2.09	0.007

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

levels and is well tolerated can improve both compliance and persistency. The present study compared rates of discontinuation and change across several ocular hypotensive therapies to determine whether any demonstrates superior persistency.

Results show that patients treated initially with tim-

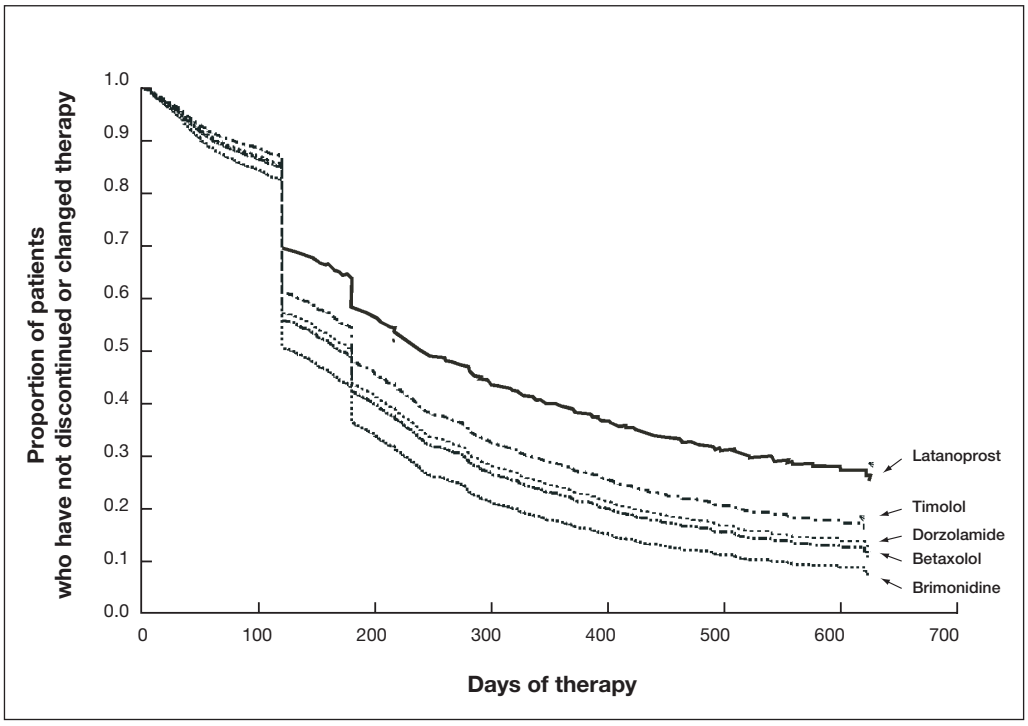

Fig. 2 - *Plot of survival function for time to discontinuation or change; adjusted Cox regression model.*

olol, brimonidine, betaxolol, or dorzolamide are more likely both to discontinue therapy and to discontinue or change therapy than those receiving latanoprost. These results were confirmed in analyses adjusted for age and sex. The significantly reduced risks of discontinuing or discontinuing/changing therapies associated with latanoprost use are consistent with results of three similar retrospective cohort studies of persistency with antiglaucoma medications (Tabs. V and VI) (14-16). These previous studies included adult (younger than 65 years of age) members of several managed care plans; each study included more than 1000 patients, and follow-up periods ranged from 18 to 30 months. In all instances, Cox regression models and survival analyses revealed that patients treated initially with latanoprost monotherapy demonstrated greater persistency compared with those treated with beta-blockers, brimonidine, or carbonic anhydrase inhibitors. Results of the current and three previous studies were uniform across outcomes (discontinuation or discontinuation/change of therapy) and stable when analyses were adjusted for age and sex. It is of interest to note that the inclusion of patients 65 years of age and older in the present study did not affect overall findings.

Although the reasons for increased persistency with latanoprost were not a subject of investigation in any of these retrospective studies, several hypotheses are proposed. For example, the higher persistency rates in patients treated initially with latanoprost may reflect clinical findings that latanoprost reduces IOP levels more effectively than timolol (8, 9, 18), brimonidine (19-21), or dorzolamide (22); no head-to-head efficacy study of latanoprost versus betaxolol has been reported. Most failures in timolol treatment reportedly occur within the first 6 months (23), but IOP drift has not been reported in patients treated with latanoprost for either 6 (8, 9, 18) or 12 months (24). In addition, systemic side-effects have been shown to occur less frequently with latanoprost than with timolol (18) or brimonidine (21). Finally, the convenience of once-daily administration with latanoprost may encourage better persistency; reduced numbers of instillations have been associated with improved compliance with topical ocular hypotensives (12, 25), and this benefit may extend beyond compliance to persistency.

As with the three previous retrospective cohort studies of persistency (14-16), the present research has both strengths and weaknesses. An important

TABLE V - RELATIVE GLAUCOMA *DISCONTINUATION* RATES IN FOUR PERSISTENCY STUDIES

		Latanoprost	Timolol	Betaxolol	Any beta-blocker	Brimonidine	CAIs
Authors/ follow-up period	**Adjusted/ unadjusted analysis**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**
Current study; 21 months	Unadjusted	1.00 [683]	1.78 (1.51, 2.10) [1408]	2.10 (1.63, 2.70) [164]	n.a.	1.68 (1.36, 2.08) [523]	1.62 (1.09, 2.40) [72]
	Adjusted (age/sex)	1.00 [683]	1.77 (1.50, 2.09) [1408]	2.14 (1.66, 2.75) [164]	n.a.	1.67 (1.35, 2.06) [523]	1.71 (1.15, 2.54) [72]
Dasgupta et al (14); 2 years	Unadjusted	1.00 reference [320]	n.a.	n.a.	1.63 (1.26, 2.11) [785]	2.26 (1.60, 3.19) [178]	2.37 (1.40, 4.03) [47]
Shaya et al (15); 30 months	Unadjusted	1.00 reference [858]	1.36 (1.28, 1.43) [939]	n.a.	n.a.	1.54 (1.44, 1.63) [486]	n.a.
	Adjusted (age/sex)	1.00 reference [858]	1.34 (1.27, 1.41) [939]	n.a.	n.a.	1.54 (1.45, 1.62) [486]	n.a.
Spooner et al (16); 18 months	Unadjusted	1.00 reference [242]	1.73 (1.40, 2.15) [547]	1.63 (1.20, 2.21) [111]	n.a.	1.70 (1.22, 2.34) [106]	n.a.
	Adjusted (age/sex)	1.00 reference [242]	1.67 (1.36, 2.06) [547]	1.53 (1.15, 2.07) [111]	n.a.	1.72 (1.25, 2.35) [106]	n.a.

CAIs=Carbonic anhydrase inhibitors (including dorzolamide); CI=Confidence interval; n=Number of patients; n.a.=Not available; RR=Hazard rate ratios from Cox regression models. [Adapted with permission from the Am J Manag Care (13)]

TABLE VI - RELATIVE GLAUCOMA THERAPY *DISCONTINUATION OR CHANGE* RATES IN THREE PERSISTENCY STUDIES

		Latanoprost	Timolol	Betaxolol	Any beta-blocker	Brimonidine	CAIs
Authors/ follow-up period	**Adjusted/ unadjusted analysis**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**	**RR (95% CI) [n]**
Current study; 21 months	Unadjusted	1.00 [683]	1.36 (1.19, 1.56) [1408]	1.58 (1.27, 1.95) [164]	n.a.	1.88 (1.61, 2.20) [523]	1.49 (1.09, 2.03) [72]
	Adjusted (age/sex)	1.00 [683]	1.36 (1.19, 1.55) [1408]	1.60 (1.29, 1.98) [164]	n.a.	1.87 (1.60, 2.19) [523]	1.53 (1.12, 2.09) [72]
Dasgupta et al (14); 2 years	Unadjusted	1.00 reference [320]	n.a.	n.a.	1.24 (1.02, 1.50) [785]	2.41 (1.89, 3.07) [178]	2.22 (1.49, 3.29) [47]
Spooner et al (16); 18 months	Unadjusted	1.00 reference [242]	1.40 (1.17, 1.68) [547]	1.36 (1.06, 1.76) [111]	n.a.	1.92 (1.50, 2.47) [106]	n.a.
	Adjusted (age/sex)	1.00 reference [242]	1.40 (1.17, 1.67) [547]	1.38 (1.07, 1.78) [111]	n.a.	1.92 (1.49, 2.46) [106]	n.a.

CAIs=Carbonic anhydrase inhibitors (including dorzolamide); CI=Confidence interval; n=Number of patients; n.a.=Not available; RR=Hazard rate ratios from Cox regression models. [Adapted with permission from the Am J Manag Care (13)]

strength of electronic claims review is the ability to include large numbers of patients, providing sufficient power to detect differences in persistency among therapies. Also, external validity is enhanced when patients are evaluated in an actual care environment rather than in a controlled experimental setting. Outcomes

measured in actual care settings are not biased by factors associated with clinical trials, such as regimentation of therapy or patients' perceptions of clinicians' expectations concerning adherence to therapeutic protocols. Further, persistency is a critical process-of-care measure that provides an essential link between the selection of a treatment by the clinician and the effectiveness of the therapy, especially in chronic conditions such as glaucoma. Thus, patients who do not fill their prescriptions cannot receive adequate therapy, and lack of persistency over time becomes a *de facto* withdrawal of the treatment itself.

Potential weaknesses of this study include the fact that patients were not required to have an ICD-9 diagnosis of glaucoma for inclusion; however, other research shows that most patients prescribed a topical ocular hypotensive do indeed have a diagnosis of glaucoma (26). As with all studies based on retrospective claims data, incomplete records and physician dispensing of product samples could have affected results. Also, patient or physician reasons for discontinuing or changing therapy were not available and would require reviews of patients' medical records or personal interviews. We can speculate that therapy changes are driven primarily by physicians' efforts to improve patients' conditions and reflect considerations of a medication's effectiveness and tolerability. Conversely, decisions to discontinue therapy are more likely to be made by patients and to reflect issues of tolerability, cost, convenience, and the asymptomatic nature of early-stage glaucoma.

The fact that the present analysis studied single events contributed to the discrepancy between the 38.8% discontinuation rate and the smaller 18.6% change rate. Our definition of medication discontinuation did not allow an evaluation of later returns to therapy in patients discontinuing the index drug. Nevertheless, we have found in unpublished work using the same methodology that most such patients resume some ocular hypotensive therapy, typically the same one, after a considerable gap between refills and that such therapeutic lapses are more common than therapeutic changes (Informagenics, LLC, unpublished data, October 2002). Whether patients tend to resume therapy of their own volition or at the urging of their physicians (who may not know for some time that discontinuation of therapy has occurred) requires further study.

Here, as in previous studies (14-16), patients initially treated with latanoprost monotherapy have been shown to be more persistent than those who begin treatment with beta-blockers, brimonidine, or carbonic anhydrase inhibitors, such as dorzolamide. Greater persistency with an initial ocular hypotensive therapy may reduce long-term costs to patients and managed care plans by limiting the increased resource use associated with discontinuations or changes in therapy (27). Over time, lack of persistency in patients with chronic conditions is the same as withdrawal of therapy. In glaucoma patients, lack of persistency may lead, at best, to increased costs associated with switching therapies and, at worst, to elevated IOP levels, disease progression, and the potentially substantial treatment costs related to the condition's worsening. These factors might be important to ophthalmologists as they select an initial ocular hypotensive for their glaucoma patients and to health service and health plan managers as they compare the economic value of various therapies.

CONCLUSIONS

Patients initially treated with latanoprost monotherapy are more persistent than those who begin treatment with beta-blockers, brimonidine, or the carbonic anhydrase inhibitor dorzolamide. Greater persistency with an initial ocular hypotensive therapy may improve health outcomes and reduce long-term costs to patients and health plans by limiting the increased resource use associated with discontinuations or changes in therapy.

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Reprint requests to:
Gregory Reardon, PhD, RPh
Informagenics, LLC
500 W. Wilson Bridge Road, Suite 115
Worthington, OH, 43085, USA
greardon@informagenics.com

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