

An Economic Analysis of Switching to Latanoprost from a β -Blocker or Adding Brimonidine or Latanoprost to a β -Blocker in Open-Angle Glaucoma or Ocular Hypertension

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Abstract

Background: In treating patients with ocular hypertension or primary open-angle glaucoma, if a single agent cannot successfully control the pressure, additional medications may be prescribed. The cost of treatment may become expensive, especially with multiple drug therapy. Thus, prescribing techniques that help minimize costs may be beneficial to patients when medically appropriate.

Objective: To evaluate differences in drug and visit costs after switching to latanoprost 0.005% monotherapy (LM) versus adding latanoprost 0.005% once daily (L β) or brimonidine 0.2% twice daily (B β) in patients uncontrolled on β -blocker therapy alone.

Methods: This study included 148 consecutive qualified charts of open-angle glaucoma or ocular hypertension patients within the first year of follow-up after switching from β -blocker monotherapy to latanoprost or adding latanoprost or brimonidine.

Results: The B β group demonstrated the highest costs per month, followed by the L β group, then the LM group. A trend existed in the L β group to a lower pressure than the B β or the LM groups. A greater mean change in medication per patient per month was seen in the B β group compared to the latanoprost treatment groups. Additionally, a greater number of visits per month occurred in the B β than in the LM and L β groups. The B β group also reported significantly more tearing and fatigue.

Conclusions: This study suggests that in patients uncontrolled on β -blocker therapy, switching to latanoprost, when medically appropriate, may provide a further mean reduction in intraocular pressure and save costs compared to adding latanoprost or brimonidine.

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Patients with ocular hypertension or primary open-angle glaucoma are generally first treated medically to reduce the intraocular pressure (IOP). If a single agent cannot successfully control the IOP, additional medicines may be prescribed as required. If medical treatment is unable to control the IOP, laser or conventional surgical methods may be considered.¹⁻² Despite the benefits of medical therapy for glaucoma, its cost may become expensive, especially with multiple drug therapy.³⁻⁴ Consequently, prescribing techniques that help minimize costs may be beneficial to patients when medically appropriate.

Previous work by Smith et al⁵ has shown a 70% success rate when using latanoprost to simplify the previous medical therapy. Many of these patients demonstrated similar or improved ocular hypertension control even when 2 or 3 medications were discontinued and replaced with latanoprost alone. Such a reduction in medications should result in a lower cost of treatment to patients.³ Consequently, for a patient who demonstrates uncontrolled IOP on β -blocker therapy alone, switching to latanoprost as opposed to adding another antiglaucoma medication may control the IOP as well as reduce cost, as the patient will only need 1 medication. Unfortunately, little information is available that analyzes the cost of switching to latanoprost versus adding adjunctive therapy to a β -blocker.

The purpose of this article is to evaluate the differences in direct costs in patients who were using β -blocker therapy alone, then had either latanoprost once daily or brimonidine twice daily added or were switched to latanoprost monotherapy.

Materials and Methods

Sample Population. Consecutive (alphabetical or numerical) patient records were reviewed from offices of ophthalmologists with large glaucoma practices in Charleston, South Carolina and Atlanta, Georgia. This study included records only from those patients who were prescribed a topical β -adrenergic blocker as monotherapy then switched to latanoprost 0.005% once daily, or had either brimonidine 0.2% twice daily or latanoprost added and had at least 1 follow-up visit after the change in therapy. Information required for this study was taken from each glaucoma-related visit in the patient's source documentation.

Subjects must have fulfilled the following conditions to have been included in this trial: be 18 years of age or older, have a clinical diagnosis of open-angle glaucoma (primary, pigmentary, or exfoliation glaucoma) or ocular hypertension in at least 1 eye (study eye), and have had a β -adrenergic blocker prescribed as monotherapy once or twice daily for at least 1 day, then substituted with latanoprost 0.005% once daily (latanoprost monotherapy) or added brimonidine 0.2% twice daily (brimonidine + β -blocker) or latanoprost 0.005% once daily (latanoprost + β -blocker), between 1996 and 12 months before the beginning of this trial (January 2001). To assure balanced numbers for each group, a 2:1 randomization between groups was used.

Patients with any of the following conditions were excluded from this trial: any abnormality preventing reliable applanation tonometry in study eye(s), media opacity preventing reliable baseline optic nerve or visual field evaluation, intraocular conventional surgery, or laser surgery within 3 months before the β -blocker therapy was changed (baseline examination), a diagnosis of primary acute or chronic angle closure, or secondary as

well as congenital glaucoma, known occludable angles by gonioscopy, presence of any other clinically significant known angle abnormality, or use of more than 1 other glaucoma medicine at the baseline visit.

Study Methods. Historical data collected included: patient age, race, sex, medical history, and prescribed β -blocker therapy. Clinical data collected for up to 6 months before and 12 months (or visit closest to 12 months) after changing β -blocker therapy included: study treatment initiated, eye treated, number of glaucoma-related visits, number of changes in glaucoma medicines, length of time on study treatment only, total follow-up time to study termination, as well as IOPs at baseline, last on-study-treatment visit (last visit that the study treatment regimen was used before any further therapy was added), and final follow-up visit (at study termination; additional treatment to control the IOP may have been added). Additional medications prescribed or surgeries performed to control the IOP were noted. In addition, all adverse events potentially related to study medicines were recorded. Only 1 randomly chosen eye from each subject was evaluated in this study.

Assessed costs for this study were based on glaucoma medicines prescribed and glaucoma related examinations (direct costs). The following formula was used to determine cost per month:

$$\text{Cost per month} = (\text{cost per bottle} \times 30 \text{ days}) \div \text{days of therapy}$$

$$\text{Days of therapy} = \text{bottle volume} \div (\text{2 eyes} \times \text{doses per day} \times \text{drop volume})$$

The cost of medicines was determined from a standard published source for average wholesale price.⁶ Costs were calculated for medicines based on both eyes receiving treatment at the usual clinical dosing schedules (ie, nonselective β -blockers as well as brimonidine given

twice daily and β -blocker gel products as well as latanoprost given once daily). Perfect compliance was assumed. The bottle volume was taken as it appeared on the label and the drop volume used was based on previous literature.³⁻⁴

Patient visit reimbursement costs were determined from a standard table for office visits and procedures (direct costs).⁷ Direct costs of additional office visits and tests due to adverse events in the study eye also were determined. These costs reflected the expenses to the insurer. No indirect costs were assessed (eg, staff time or additional out-of-pocket expenses to the patient).

Statistical Analysis. One hundred forty-eight patients were entered in order to have at least 37 patients enrolled in each treatment group, and up to a 2:1:1 admission ratio was allowed if necessary. All analyses were 2-sided and a 5% probability level was used to declare significance.

Not all patients had an exact 12-month follow-up period. Consequently costs, visits, and medicine changes were assessed on a per month basis. Differences between groups for the primary efficacy variable, costs per month, were evaluated with a 1-way analysis of variance (ANOVA) test. In addition, the secondary efficacy variables, age, IOP, number of visits per month,

number of changes in medicine per month, length of time in study (and percent time), number of visits, and length of time that patients remained on the study treatment regimen only, were analyzed by a 1-way ANOVA test.⁸ Analyses between individual pairs of treatment groups were performed by an unpaired *t*-test within the ANOVA using the least squares method.⁹

Adverse events, race, sex, specific study as well as treated eye, β -blocker therapy, and the difference between groups in success rate were analyzed by a chi-square test.⁸ Definition of success of therapy was defined by those criteria found in Table 1.

Results

Patients. The characteristics of patients included in this study are found in Table 2. No statistical differences were observed between groups for age, sex, race or β -blocker prescribed. Statistical differences were noted between groups in both the treated eye (*P* = .034) and the study eye (*P* = .018).

IOP. The treatment results data are found in Table 3. At baseline (β -blocker treatment only) no statistical difference was noted between treatment groups. However, the group to be treated with bri-

Table 1. Patient's Clinical Response to Therapy, n (%)

	IOP Controlled	Therapeutic Success	Latanoprost Monotherapy (n = 37)	Latanoprost + β -Blocker (n = 74)	Brimonidine + β -Blocker (n = 37)	P Value
Study treatment only and ≥ 2 mm Hg decreased IOP*	Yes	Yes	20 (54%)	52 (70%)	18 (49%)	.056
Study treatment only and < 2 mm Hg decreased IOP	No	No	13 (35%)	13 (18%)	9 (24%)	.12
Adverse event causing discontinuation	n.a.	No	3 (8%)	5 (7%)	7 (19%)	.13
Additional therapy required	No	No	1 (3%)	4 (5%)	3 (8%)	.57

IOP=intraocular pressure; n.a.=not applicable

*Therapy will still be a success if patient undergoes nonglaucoma intraocular surgery before (ie, cataract surgery) and the IOP is controlled on last preoperative visit.

Table 2. Patient Characteristics

	Latanoprost Monotherapy (n = 37)	Latanoprost + β -Blocker (n = 74)	Brimonidine + β -Blocker (n = 37)	P Value
Age (years), mean \pm SD	72.8 \pm 13.7	75.2 \pm 11.6	76.4 \pm 10.2	.39
Gender, n				
Male	16	31	14	.80
Female	21	43	23	
Race, n				
Caucasian	27	42	24	.23
African American	10	30	12	
Hispanic	0	2	1	
Treated eye(s), n				
Right	4	10	4	.034
Left	2	5	10	
Both	31	59	23	
Study eye, n				
Right	26	42	14	.018
Left	11	32	23	
β -Blocker therapy, n				
Timolol	25	52	24	.89
Carteolol	5	9	4	
Levobunolol	3	8	5	
Betaxolol	3	5	3	
Metipranolol	1	0	1	

monidine + β -blocker was almost 1 mm Hg higher in baseline IOP than the groups to be treated with latanoprost.

At the last on-study-treatment visit, no statistical difference in IOP was noted between groups ($P = .078$). However, a trend was observed for patients in the latanoprost + β -blocker therapy group to have the lowest IOP.

At the final follow-up visit, all 3 groups were controlled to a statistically similar mean IOP average ($P = .076$). However, a trend was again noted for those patients treated with latanoprost + β -blocker to have a lower IOP. In addition, the change in IOP between groups from baseline was statistically similar for both the last on-study-treatment visit ($P = .38$) and after 12 months ($P = .23$). However, a trend to a slightly less hypotensive change existed with the latanoprost monotherapy group.

Treatments and Visits. The average time that patients in each group remained

on the study treatment compared to the total time of follow-up was not statistically different among groups, although a trend existed for the brimonidine + β -blocker group to have the shortest percent time on this treatment ($P = .10$) (Table 3). In a paired comparison, the brimonidine + β -blocker group showed a shorter time period on the study medicine than the latanoprost + β -blocker group ($P = .03$).

Until the final follow-up visit the number of medicine changes per month during the follow-up time was higher and statistically significant in the brimonidine + β -blocker group and lowest in the latanoprost monotherapy and latanoprost + β -blocker groups ($P = .001$). Additionally, the average number of visits per month for the first year following baseline was statistically greater in the brimonidine + β -blocker group ($P = .05$) (Table 3).

The number of patients who had a change in therapy to control the IOP was low in all 3 treatment groups ($P = .57$)

Table 3. Treatment Results, Mean ± SD

	Latanoprost Monotherapy	Latanoprost + β-Blocker	Brimonidine + β-Blocker	P Value
IOP at baseline (mm Hg)	20.9 ± 4.9	20.9 ± 4.3	21.7 ± 6.3	.71
IOP at last on-study-treatment visit*	18.0 ± 3.0	16.5 ± 3.8	17.8 ± 4.4	.078
IOP at final follow-up visit†	18.0 ± 2.9	16.4 ± 4.0	17.1 ± 4.1	.076
IOP change from baseline to last on-study-treatment visit	2.9 ± 5.1	4.4 ± 5.1	3.9 ± 5.5	.38
IOP change from baseline to final follow-up visit	2.8 ± 4.6	4.5 ± 5.5	4.6 ± 5.2	.23
Number of medicine changes/person/month	0.01 ± 0.03	0.01 ± 0.06	0.04 ± 0.06	.001
Number of visits/person/month	0.36 ± 0.20	0.38 ± 0.20	0.46 ± 0.22	.05
Total number of visits	3.8 ± 2.0	4.2 ± 1.5	4.5 ± 2.0	.16
Time on study treatment (months)	10.6 ± 4.3	11.2 ± 3.7	9.4 ± 4.9	.10*
Time in study (months)	11.6 ± 3.7	12.1 ± 3.0	11.2 ± 4.5	.45

IOP=intraocular pressure.

*Last day the study regimen was used alone before any further therapy was added.

†P value from the unpaired t-test within the analysis of variance (ANOVA) was significant (0.03).

*From baseline to study termination (may have included additional therapy to control the intraocular pressure).

(Table 1). Two patients required laser surgery (1 in the latanoprost + β-blocker group and 1 in the brimonidine + β-blocker group), and no patients required conventional surgery during the 1-year follow-up period. One patient (latanoprost + β-blocker group) required 3 or more medicines to control the IOP.

Based on the definitions for success of therapy in Table 1, a trend between groups was observed, indicating that the latanoprost + β-blocker group was the most successful and the brimonidine + β-blocker group was the least successful ($P = .056$). The reasons for success or nonsuccess are given in Table 1.

Adverse Events. Ocular and systemic adverse events are shown in Table 4 and Table 5, respectively. The brimonidine + β-blocker group showed a greater incidence of fatigue ($P = .048$) and ocular tearing ($P = .027$).

Cost of Therapy. The cost analyses are

presented in Table 6. No significant difference was noted among groups in the cost per person per month of therapy 6 months prior to enrollment ($P = .27$). However, the brimonidine + β-blocker group demonstrated a trend to a higher cost of therapy than the 2 groups that received latanoprost. Following the baseline measurements, a statistical difference in direct costs per month (patient visits and drug costs) was observed between groups until the final follow-up visit ($P = .038$). The latanoprost monotherapy group demonstrated lower total direct costs for the study period than the latanoprost + β-blocker group and the brimonidine + β-blocker treatment group ($P < .001$).

Discussion

Latanoprost was released in 1996 as an ocular hypotensive agent. Latanoprost is an analog of an F_{2a} prostaglandin and is highly selective for the FP-receptor.¹⁰ Several studies have indicated that the mechanism of action of the IOP reduction

Table 4. Ocular Adverse Events (3 or More Events), n (%)

	Latanoprost Monotherapy (n = 37)	Latanoprost + β -Blocker (n = 74)	Brimonidine + β -Blocker (n = 37)	P Value
Blurred vision	10 (27)	15 (20)	12 (32)	.62
Allergy	4 (11)	16 (22)	8 (22)	.35
Tearing/watering	5 (14)	9 (12)	12 (32)	.027
Conjunctival hyperemia	4 (11)	10 (14)	3 (8)	.69
Burning/stinging	3 (8)	2 (3)	5 (14)	.095
Mucus/runny discharge	3 (8)	2 (3)	4 (11)	.20
Blepharitis	1 (3)	5 (7)	2 (5)	.67
Ocular pain	2 (5)	3 (4)	3 (8)	.67
Foreign body sensation	—	5 (7)	2 (5)	.28
Dryness	3 (8)	1 (1)	1 (3)	.17
Irritated lids	1 (3)	2 (3)	—	.60
Total adverse events	36	70	52	—
Total number of patients having adverse events	21 (57)	41 (55)	22 (59)	.79

by latanoprost is increased uveoscleral outflow.¹¹⁻¹⁴ When compared to timolol maleate given twice daily, latanoprost 0.005% once daily has demonstrated either an equal or statistically greater reduction in IOP for as long as 6 months in American and Scandinavian multicenter studies.¹⁵⁻¹⁶ Side effects that have been described have been iris color darkening, eyelash growth, and conjunctival hyperemia.¹⁵ A possible association to uveitis, recurrent corneal herpes keratitis, and cystoid macular edema also may exist in some patients.¹⁷⁻¹⁹

Brimonidine 0.2% was also released commercially in 1996. It is a relatively selective α_2 -adrenergic agonist and reduces the IOP primarily by suppressing aqueous formation.²⁰ When given twice daily it reduces the IOP at morning trough approximately 16% from baseline.²¹⁻²² Brimonidine has been shown to have similar trough efficacy to both betaxolol and dorzolamide.²³⁻²⁴ Brimonidine also may cause side effects, including ocular allergy with an incidence of approximately 10%,

typically presenting 3 months or later after initiation of therapy.²² Additionally, systemic side effects of dry mouth, fatigue, and blood pressure changes may occur.²⁵⁻²⁶

When compared directly, Stewart et al²⁷ showed that latanoprost caused a lower IOP than brimonidine at every 2-hour time point between 08:00 and 20:00 hours. Additionally, brimonidine twice daily did not lower the pressure from baseline for the full daytime 12-hour dosing cycle.

The purpose of this study was to evaluate the cost of therapy in the first year after changing therapy from a β -blocker monotherapy to latanoprost alone or adding latanoprost or brimonidine twice daily adjunctively to β -blocker monotherapy.

Study findings indicated that within the first 12 months following the initiation of the 3 different study treatments, cost was significantly reduced in the latanoprost monotherapy group compared to both adjunctive treatment groups. After switching to latanoprost, the average cost of physician visits and pharmaceutical thera-

Table 5. Systemic Adverse Events

	Latanoprost Monotherapy (n = 37)	Latanoprost + β -Blocker (n = 74)	Brimonidine + β -Blocker (n = 37)	P Value
Headaches	1	2	—	.60
Worsened allergies	1	—	2	.15
Irregular heartbeat	1	—	—	.22
Fatigue	—	—	2	.048
Dizziness	—	1	—	.61
Shortness of breath	1	—	—	.23
Bradycardia	—	—	1	.23
Total adverse events	4	3	5	.18
Total number of patients having adverse events	4	3	3	.38

Table 6. Cost Analyses per Person in US Dollars, Mean \pm SD (95% Confidence Intervals)

	Latanoprost Monotherapy	Latanoprost + β -Blocker	Brimonidine + β -Blocker	P Value
Number of patients	37	74	37	
Cost/person/month pre-enrollment*	66.71 \pm 99.80 (33.44-99.99)	53.98 \pm 19.12 (49.55-58.51)	75.67 \pm 92.45 (44.85-106.50)	.27
Cost/person/month post-enrollment	53.63 \pm 11.95 (49.64-57.61)	83.19 \pm 79.29 (64.82-101.56)	106.20 \pm 134.59 (61.32-151.07)	.038
Total difference in cost/person/month from pre-enrollment to post-enrollment	-13.08 \pm 101.08 (-46.79-20.62)	29.21 \pm 81.52 (10.33-48.10)	30.53 \pm 134.43 (-14.30-75.35)	.090

* β -blocker only.

py per month was \$53.63 for patients treated with latanoprost monotherapy, whereas latanoprost + β -blocker cost \$83.19 and brimonidine + β -blocker, \$106.20. The cost of the latanoprost monotherapy group actually decreased by \$13 per month from that of β -blocker therapy monotherapy. The additional medical therapy apparently increased the costs in the adjunctive treatment group. In addition, the latanoprost-treated group showed a lower rate of each of the following: changes in medication to control IOP,

patient visits per month, and certain adverse events (tearing and fatigue). These factors may have helped limit costs in these groups.

All groups demonstrated a statistically reduced pressure from baseline. The IOP control was similar between groups at the last on-study-treatment visit. However, the latanoprost + β -blocker group demonstrated a trend to have lower pressures than the latanoprost monotherapy group or the brimonidine + β -blocker group. This study was not sufficiently powered

statistically to evaluate IOP for a parallel designed trial, and the times in which pressures were measured throughout the day were not controlled.

Following adjustments to therapy for uncontrolled IOP at 1 year, all 3 groups had a similar mean IOP. Two patients required laser surgery during the 1-year follow-up period (1 in the latanoprost + β -blocker and 1 in the brimonidine + β -blocker groups). No patient required 4 or more medicines or conventional surgery to control the pressure.

Regarding the percent of time on the original study treatment regimen, no significant difference was noted between groups, but the latanoprost-treated groups demonstrated a trend to the greatest survival time on the original treatment. However, the latanoprost + β -blocker group, in a paired comparison, showed a greater survival time on the original study treatment than the brimonidine + β -blocker group.

The data in this study may help clinically when physicians consider a patient who is uncontrolled on a β -blocker alone. Switching this patient to latanoprost should further reduce the IOP (≥ 2 mm Hg) in approximately 50% of cases. Nonetheless, the pressure response may not quite reach the reduction gained by adding latanoprost or brimonidine. However, switching to latanoprost may save the patient approximately 33% to 50% in treatment costs for the first year and limit some adverse events, changes in medicine, and patient visits compared with β -blocker and brimonidine treatment.

This study suggests that in patients uncontrolled on β -blocker therapy, switching to latanoprost when medically appropriate may provide a further mean reduction in IOP and save costs compared to adding latanoprost or brimonidine adjunctively.

This study was retrospective in design; consequently, more information on a prospective basis is required regarding costs and frequency of visits and medicine changes. In addition, the study contained only a short-term (1 year) follow-up of patients and could not effectively evaluate visual field and optic disc changes long-term (5 years or longer) associated with

these medications. Future research will further clarify differences among treatment groups regarding cost and convenience of therapy.

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