ELSEVIER

# Achieving Low Target Pressures With Today's Glaucoma Medications

**Louis Cantor, MD**

*Indiana University School of Medicine, Indianapolis, Indiana, USA*

**Abstract.** In the 21st century there are more highly effective medical management options for glaucoma than there were in the 1980s and 1990s. In deciding among them, the clinician's challenge is to select what is clinically relevant from the large amounts of available data. In evaluating different drugs the clinician must consider not only the mean intraocular pressure (IOP) of a trial population, but also the percentage of patients achieving clinically relevant low IOPs. The consistency of IOP control throughout the day and night is also critical. Other factors such as safety, tolerability, and cost-effectiveness must also be kept in mind, with an awareness (both in human and monetary terms) of the cost of treatment failure. This overview concludes that newer medical regimens for IOP lowering address efficacy and safety issues more successfully than older ones. (**Surv Ophthalmol 48 [Suppl 1]**: S8–S16, 2003. © 2003 Elsevier Science Inc. All rights reserved.)

**Key words.** glaucoma medications • intraocular pressure

## Introduction

A large body of evidence has established the importance of intraocular pressure (IOP) reduction in the medical management of glaucoma. Other targets for therapeutic intervention, such as improving the facility of aqueous outflow, improving ocular blood flow, and direct neuroprotection of retinal ganglion cells, are under investigation, but IOP lowering remains the primary goal of all glaucoma treatment strategies. Recent studies have shown that IOP levels once considered to be safe (near 17 or 18 mm Hg) do not prevent progressive visual field loss in many patients.[2] This supports increasingly aggressive efforts to get IOP as low as safely possible, especially in patients with severe or rapidly progressing disease.

Physicians have been prescribing IOP-lowering medications for nearly 150 years.[16,50] Von Graefe advocated the use of atropine to lower IOP in glaucoma patients as early as 1856, although by 1868 his research showed that the drug did more harm than good. Miotics, such as eserine and pilocarpine, were first introduced as glaucoma therapy in 1864 and 1875, respectively. Epinephrine was used in glaucoma patients as early as 1899. Cholinergic agents (introduced in the 1940s) were more effective at lowering IOP than pilocarpine was, but they had concomitantly more severe side effects. The first systemic carbonic anhydrase inhibitor to be used for glaucoma, acetazolamide, was introduced in 1954. The topical beta-blocker timolol maleate became available in 1978, and the $\alpha_2$-adrenergic agonists, apraclonidine and brimonidine, were introduced in 1987 and 1996, respectively. New glaucoma medications have been introduced since the late 1990s. Dorzolamide (Trusopt, Merck, West Point, PA), a carbonic anhydrase inhibitor, became available in 1995; latanoprost (Xalatan, Pharmacia, Peapack, NJ),





0039-6257/03/$–see front matter
doi:10.1016/S0039-6257(03)00009-2

a prostaglandin analog, in 1996; the timolol/dorzolamide fixed combination (Cosopt, Merck, West Point, PA) in 1998; and travoprost (Travatan, Alcon, Ft Worth, TX), a prostaglandin analog, the timolol/latanoprost fixed combination (Xalcom, Pharmacia, Peapack, NJ), and bimatoprost (Lumigan, Allergan, Irvine, CA), a prostamide, all in 2001.

With this large armamentarium of IOP-lowering medications, the challenge is to decide which medication will be most effective with which patient, with the best side effect profile. This review will discuss the most clinically relevant criteria for distinguishing among the available treatment options and how specific medications fulfill these criteria.

## Criteria for Evaluating Glaucoma Medications

In determining which medication would best meet a patient's needs, the physician must consider overall drug efficacy, safety, and tolerability first. Other issues, however, should also be considered to a greater or lesser degree depending on the patient. For example, factors affecting compliance (such as inconvenient dosing regimens) may be an issue for some patients. In addition, the ability of a drug to perform well in different subcategories of patients is important. In particular, there is evidence that both surgical and medical treatments are more likely to fail in patients of African descent than in other patients, leading to higher rates of blindness.[3,37,56] Cost issues should be considered last and carefully because a comparison of direct drug costs may not accurately reflect the comparative overall treatment costs of drugs with widely different efficacy and safety profiles.

### EFFICACY

Several measures are used to evaluate IOP-reducing efficacy. The most commonly used benchmark is the mean IOP decrease in the treated population as a whole. This number is what the Food and Drug Administration and international agencies use during the regulatory evaluation of new glaucoma drugs. This is an important piece of information, but it does not convey the treatment success and failure rates associated with each drug, namely, the percentage of patients who do or do not achieve a clinically beneficial low IOP.

The Ocular Hypertension Treatment Study (OHTS) demonstrated that lowering IOP by 20% from baseline delays or prevents the onset of glaucomatous damage in OHT patients.[27] The AGIS-7 study demonstrated that patients with an IOP consistently above 17.5 mm Hg over their first three 6-month visits experienced rapidly progressing disease over the subsequent 6 years.[2] Clinicians frequently individualize a desired IOP range as a goal of glaucoma therapy.[53] Consequently, studies that report the percentage of patients who reached several different target pressures allow for a more in-depth comparison of IOP-lowering efficacy. In the AGIS-7 study, patients with IOP consistently ≤18 mm Hg at every visit over the 6-year follow-up period experienced a mean change from baseline in visual field defect score close to zero.[2] (A more thorough discussion of the importance of maintaining a low IOP can be found in the article by Goldberg in this supplement.[23])

The degree of IOP control throughout the day and night is another important indication of drug efficacy. IOP is known to have a typical circadian rhythm, with greater than normal fluctuations in glaucoma patients.[6] In a study of 64 patients who performed home tonometry for 5 days, 88% of glaucoma patients with the widest diurnal variations in IOP lost visual field over time, compared to 57% of patients with the narrowest diurnal variation.[6] Consequently, the ideal glaucoma medication should ensure that IOP stays fairly constant throughout a 24-hour period.

### SAFETY AND TOLERABILITY ISSUES

Safety and tolerability issues tend to get classified together under the heading "adverse events," but it is more appropriate to consider them separately. True safety issues, such as the development of cystoid macular edema, cardiopulmonary problems, or CNS effects, threaten ocular or systemic health and are obviously important to consider in making a medication choice. They may be difficult to detect without great diligence, however, or may not be the type of problem that the patient or physician would easily associate with a topical medication. Tolerability issues, such as eye redness, eyelash growth, and iris color change, are more readily apparent to both physician and patient and may cause some patients to request a change in medication. The challenge to the physician is to educate the patient about the risks associated with changing to a more tolerable but potentially less effective medication or a medication with more subtle but potentially more serious adverse effects.

### MECHANISM OF ACTION FOR IOP LOWERING

The magnitude of IOP lowering and overall treatment safety are the most important criteria for choosing a glaucoma medication, but the underlying mechanism of IOP lowering can also be important.[10] The mechanism of action can suggest how well the medication may be able to control IOP when the patient is going about his or her daily activities. Mechanism of action is also important to consider in those cases when monotherapy does not

provide sufficient IOP lowering and a second medication needs to be added.

There are two primary mechanisms for lowering IOP: decrease the amount of aqueous humor coming into the eye or increase the amount going out. It is believed that a defect in outflow leads to elevated IOP and poor IOP control. Some medications decrease the production of aqueous humor whereas others improve outflow. Aqueous humor flows out of the eye using two pathways: one that is sensitive to IOP (the trabecular meshwork pathway) and one that operates independently of IOP (the uveoscleral pathway). The trabecular meshwork pathway is important for limiting the effects of transient IOP spikes that result from normal diurnal fluctuation and daily activities; consequently, IOP-lowering drugs that increase aqueous outflow through this pathway are particularly valuable.[10]

### OTHER CONSIDERATIONS: COMPLIANCE, COST, AND HIGH-RISK PATIENTS

Factors that contribute to patient compliance with a treatment regimen include dosing frequency, the number of drugs prescribed, and the tolerability of the medication. Financial issues include acquisition cost, the indirect cost of additional time and resources to treat adverse events, and the consequences of treatment failure. Physicians also need to consider their patient's risk profile. The prevalence of glaucoma is 4.3 times higher in blacks than in nonblacks,[54] and patients of African descent with glaucoma may not respond as well to surgical or medical treatment,[1,37,41] leading to a higher risk of progression to blindness in blacks.[56] Thus, it is important to consider the efficacy of medications by race as well as in the general population.

## Evaluating the Most Commonly Used Glaucoma Medications

Medications commonly used for glaucoma patients today include timolol, a non-selective beta-blocker; latanoprost and travoprost, both prostaglandin analogs; bimatoprost, a prostamide; brimonidine, an $\alpha_2$-agonist; and the fixed combination of timolol/dorzolamide, which combines a beta-blocker with a carbonic anhydrase inhibitor in a fixed proportion.[48]

### IOP-LOWERING EFFICACY

Timolol has been widely used since its introduction in the United States in 1978.[34] Roughly half of all glaucoma patients, however, are poor candidates for timolol therapy for either efficacy or safety reasons.[30] With long-term timolol treatment, about 20–25% of patients on timolol will experience tachyphylaxis. In addition, the effectiveness of timolol may also be compromised due to drug interactions. The efficacy of timolol in lowering mean IOP is reduced if the patient is simultaneously taking systemic beta-blockers.[47] In Schuman's 12-month trial comparing the IOP-lowering efficacy of brimonidine 0.2% twice a day with timolol 0.5% twice a day, a post-hoc analysis was done to evaluate the IOP-lowering response in patients taking both topical and systemic beta-blockers (7.1% of all participants). The mean IOP reduction from baseline was smaller (at both peak and trough) in patients taking topical and systemic beta-blockers ($n = 30$) than in patients receiving topical timolol alone ($n = 341$).

Latanoprost and travoprost provide greater IOP-lowering than timolol (Fig. 1). Travoprost and latanoprost are essentially equivalent to each other.[37] In a 12-month study, travoprost once daily treatment resulted in mean IOPs at 8 AM that were 1.0–1.4 mm Hg lower than IOPs achieved with timolol twice daily ($p \leq .009$); travoprost once daily resulted in mean IOPs that ranged from 0.6 mm Hg lower to 0.4 mm Hg higher than latanoprost once daily, but none of the differences were statistically significant.[37] In one 6-month trial, latanoprost once daily lowered mean IOP more than timolol twice daily did by 0.4–0.9 mm Hg.[61] Differences in mean IOP were statistically significant only at weeks 12 ($p = 0.04$) and 18 ($p < .001$). In another 6-month study latanoprost once daily lowered IOP more than timolol twice daily by 1.2 mm ($p < .001$).[25]

Bimatoprost also provides greater IOP-lowering than timolol. In a 12-month trial, mean IOP in bimatoprost-treated patients was consistently significantly lower (by 2–3 mm Hg) than in timolol-treated patients at each measurement ($p < .001$).[26] A recently published direct comparison of bimatoprost with latanoprost[39] confirms data from two earlier studies[18,22] that suggested that bimatoprost was more effective in lowering IOP than latanoprost. The Noecker study was a well-powered, rigorously designed, multicenter, randomized, double-blind trial.[39] Bimatoprost-treated patients achieved significantly greater mean IOP reduction from baseline than did latanoprost-treated patients at every measurement and at all visits through the 6 months of treatment, even though baseline IOP with bimatoprost was slightly higher than with latanoprost.[20,39] Moreover, the published paper presented detailed data about not only the primary outcome measure (mean reduction from baseline IOP) but also several secondary outcome measures that confirmed the primary results.

Brimonidine twice daily is roughly equivalent to timolol twice daily in IOP-lowering efficacy, as shown in several studies.[29,49] Unlike timolol, the efficacy of brimonidine is not decreased by simultaneous treat-

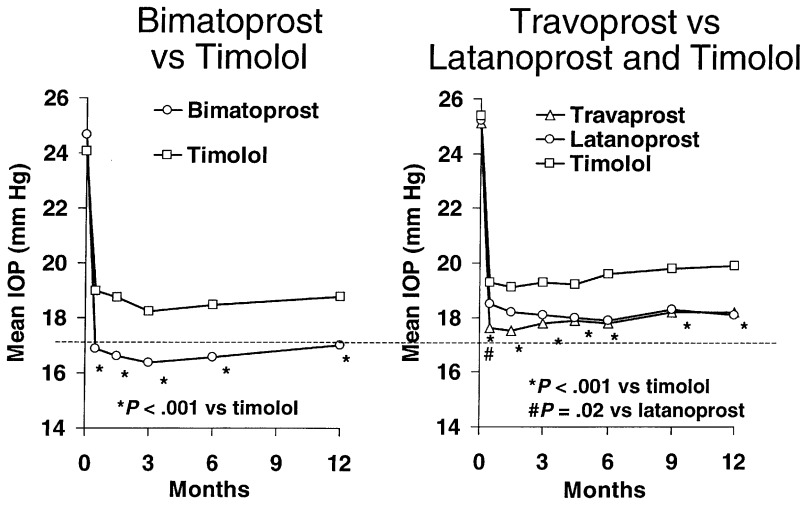



*Fig. 1. Left:* Mean IOP in participants treated with either bimatoprost 0.2% once daily (n = 474) or timolol 5.0% twice daily (n = 241) after 12 months of follow-up. IOP is statistically significantly lower in patients treated with bimatoprost once daily at all visits. (Reprinted with permission of *Archives of Ophthalmology* from Higginbotham et al.[26]) *Right:* Mean IOP in patients treated with travoprost (n = 197), latanoprost (n = 193), or timolol (n = 195) over 12 months of follow-up. IOP is statistically significantly lower in patients treated with travoprost compared with timolol at all visits ($p < .001$), and with latanoprost only at the week 2 visit ($p < .02$). (This figure was derived from data from Netland et al.[37])

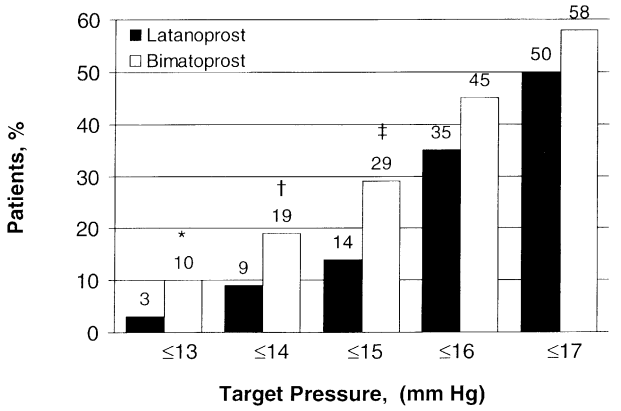
ment with systemic beta-blockers.[46] Brimonidine-purite (Allergan, Irvine, CA) 0.15%, the newly approved formulation of brimonidine preserved with purite (Allergan, Irvine, CA), has the same efficacy as brimonidine 0.2% preserved with benzalkonium chloride.[28] The lower concentration of active ingredient in brimonidine-purite 0.15% is as effective as the older formulation because brimonidine-purite's higher pH allows more brimonidine to penetrate into aqueous humor and hit the target site for lowering IOP.[4]

Clineschmidt and colleagues found that the IOP-lowering efficacy of the fixed combination of timolol/dorzolamide is statistically significantly superior to monotherapy with each component at 3 months (article reported only $p \leq .05$).[17] Data from a study by Coleman suggests that the combination drug timolol/dorzolamide is less effective than bimatoprost monotherapy (personal communication).

Data that measure the efficacy of glaucoma medications by comparing the percentage of patients reaching a specific target IOP come from studies comparing latanoprost with timolol, bimatoprost with timolol, and bimatoprost with latanoprost. Both latanoprost once a day and bimatoprost once a day performed well against timolol twice a day, with similar percentages of patients achieving targets between 13 mm Hg and 18 mm Hg.[5,26] In a 3-month direct comparison of latanoprost with bimatoprost, however, Gandolfi and colleagues found that twice as many patients achieved target pressures of 15 mm Hg or lower in the bimatoprost group (29%) than in the latanoprost group (14%) ($p = .009$)[22] (Fig. 2). In a separate 6-month direct comparison of bimatoprost with latanoprost, at month 6, mean IOP was significantly lower with bimatoprost than with latanoprost at all timepoints at all follow-up visits. In addition, the percentage of patients classified as non-responders (IOP decrease < 15%) was more than twice as high in the latanoprost group than the bimatoprost group at all times of day ($p = .001$). Patients were excluded from participating in this trial if they had received either study drug in the 2 months prior to the beginning of the trial.[39]

Timolol is known to provide poor IOP control at night and in the early morning.[42] Bimatoprost, travoprost, and latanoprost all provide much better IOP control throughout the day and night. In a comparison study of latanoprost versus bimatoprost,[22] mean IOP of patients treated with bimatoprost ranged from 17.0–17.5 mm Hg throughout the day, compared to 17.4–18.0 mm Hg with latanoprost. At 12 noon and 4 PM, the mean IOP in bimatoprost-treated patients was statistically significantly lower than in patients treated with latanoprost (Fig. 3). Travoprost and latanoprost appear to provide similar diurnal control,[37] with IOPs near 18 mm Hg between 10 AM and 4 PM in a direct comparison of these two drugs.

There is no information on how well the fixed combination of timolol and dorzolamide controls IOP throughout the day. It is reasonable to expect, how-




*P = .049 vs latanoprost.
†P = .038 vs latanoprost.
‡P = .009 vs latanoprost.

*Fig. 2.* Patients achieving specific target IOPs at noon at month 3, approximately 16 hours post dose. In a 3-month study comparing latanoprost (n = 113) with bimatoprost (n = 119), Gandolfi and colleagues found that 29% of glaucoma or OHT patients treated with bimatoprost reached target pressures of 15 mm Hg or lower; about half as many achieved that target with latanoprost (14%) (p = .009). p values for ≤ 16 mm Hg and ≤ 17 mm Hg were not significant. Patients were excluded from participating in this trial if they had received either study drug in the 2 months prior to the beginning of the trial. (Reprinted with permission of *Advances in Therapy* from Gandolfi et al.[22])

ever, that the fixed combination of timolol and dorzolamide would provide circadian control similar to that of its components alone. It is known that timolol provides poor circadian IOP control. Dorzolamide is slightly less effective than latanoprost at providing circadian control, but provides better control than timolol during the late night and early morning.[42]

## SAFETY AND TOLERABILITY ISSUES

Enough is known about the long-term systemic adverse effects of beta-blockers to cause physicians to avoid prescribing nonselective beta-blockers in roughly 12% of glaucoma patients.[30] Another 10% will be discontinued from beta-blocker therapy due to serious systemic adverse events, such as effects on the cardiopulmonary system, sexual dysfunction, and masking of hypoglycemia. In addition, timolol may affect the central nervous system, causing depression, fatigue, and forgetfulness. Timolol treatment is also associated with conjunctival metaplasia,[59] corneal anesthesia,[9] impaired tear film,[40] and a reduction in endothelial cells.[13,35] There are no major tolerability issues with timolol. Most timolol patients feel that instilling the drops is comfortable although some stinging can occur.

An important therapeutic advantage offered to patients by the prostamide and prostaglandin analogs (both known as ocular hypotensive lipids [HTLs]) is that they pose fewer systemic safety concerns than timolol does. Clinical trials indicate that, for the most part, latanoprost, travoprost, and bimatoprost do not induce significant changes in heart rate, blood pressure, pulmonary function, or laboratory values.[12,19,37] There are case studies, however, that indicate that some patients treated with latanoprost may develop hypertension or migraines.[43,62] Tolerability-related effects of prostaglandin analogs and prostamides include hyperemia, iris color change, and eyelash growth.[12,37,39,52] Conjunctival hyperemia, eyelash growth, and ocular pruritis were more common in bimatoprost-treated patients than in latanoprost-treated patients in a 6-month direct comparison ($p < .025$).[39] Discontinuation rates due to adverse events, however, were low in both the bimatoprost and latanoprost groups (4.5% and 3.7%, respectively,[39] in 4–13% of patients, depending on how allergy is defined and the duration of drug exposure).[14] Brimonidine-Purite 0.15%, the newly approved formulation of brimonidine preserved with Purite, is associated with a 41% lower incidence of ocular allergy.[28] Long-term brimonidine therapy in adults is associated with few, mostly mild, adverse events, including fatigue, headache, and dry mouth. Brimonidine is contraindicated in children under 2 years of age due to the possibility of central nervous system suppression in infants.

The timolol/dorzolamide combination shares the same safety and tolerability concerns as the component drugs do individually. Timolol is associated with cardiopulmonary and CNS effects, among other problems; dorzolamide is associated with central nervous system effects,[45] allergic conjunctivitis,[55] renal stones,[15] and irreversible corneal decompensation.[31] Timolol, as discussed, has no major tolerability issues. Dorzolamide, however, is associated with hyperemia, blepharitis, burning, stinging, and an altered sense of taste.[21,32,44]

## MECHANISM OF ACTION FOR IOP LOWERING

Each of the five main categories of drugs used for glaucoma exhibits a different mechanism of action; some affect more than one mechanism. Timolol decreases aqueous humor production.[38] Latanoprost and travoprost increase aqueous outflow via the uveoscleral pathway.[51,57]

Bimatoprost has been shown to increase outflow primarily through the trabecular-meshwork pathway, with some outflow through the uveoscleral pathway as well.[11] Brimonidine decreases aqueous humor production and increases aqueous outflow through the uveoscleral pathway.[58] In many animal models brimonidine also has demonstrated neuroprotective potential.[63,64] The timolol/dorzolamide

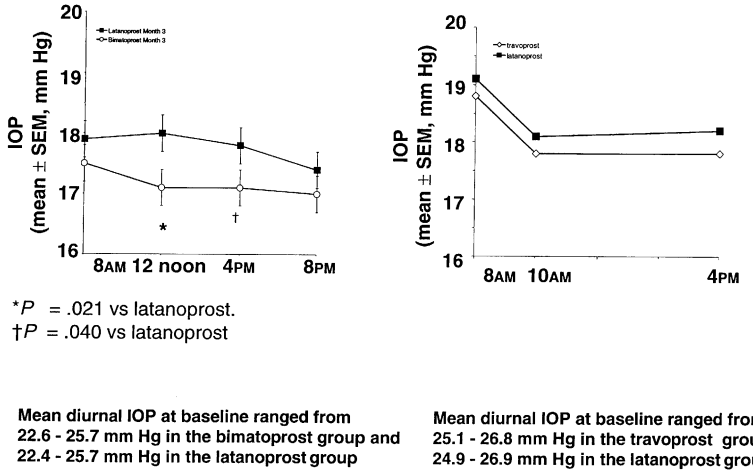



*Fig. 3. Left:* Diurnal IOP at the 3-month visit in patients receiving bimatoprost (n = 119) or latanoprost (n = 113). Mean IOP was statistically significantly lower with bimatoprost at 12 noon and 4 PM. At all times of the day bimatoprost was at least as effective or more effective than latanoprost. (Reprinted with permission from Gandolfi et al.[22]) *Right:* Mean IOP between 8 AM and 4 PM for patients treated with travoprost .004% (n = 197) or latanoprost .005% (n = 193). Travoprost and latanoprost provide roughly equivalent diurnal control. There was no statistically significant difference between the two drugs at any time point ($p > .2$). The data from which this figure was derived did not include values for standard deviation or standard error of the mean. (This figure was derived from data from Netland et al.[37])

combination decreases aqueous humor production, as do each of its component drugs.

### OTHER CONSIDERATIONS: COMPLIANCE, COST, AND HIGH-RISK PATIENTS

Patients are more likely to comply with a treatment regimen if they only have to instill eye drops once per day.[7,8,24,36] Patients and payers also appreciate lower medication costs, but this is not a simple factor to calculate. For example, although the acquisition cost is lower with timolol than with the hypotensive lipids (prostaglandins and prostamides), the less favorable safety and efficacy profiles may increase the need for additional office visits or IOP-lowering medications—all of which increase costs.

It has long been known that timolol is less effective in black than nonblack patients and this has been confirmed in recent studies.[26,37] Bimatoprost and latanoprost, in contrast, are equally effective in black and nonblack patients. In a 1-year trial, bimatoprost lowered IOP to the same extent in both black and nonblack patients, whereas timolol was less effective in black patients than in nonblack patients.[26] Travoprost, on the other hand, is less effective in lowering mean IOP in nonblack patients than in black patients. This was demonstrated in a large (n = 801) comparison of travoprost to timolol and latanoprost. Mean IOP ranged from 16.2–19.9 mm Hg among black travoprost-treated patients and from 17.8–20.0 mm Hg among nonblack travoprost-treated patients.[37]

## Glaucoma Treatment—An Evolving Paradigm

Overall, prostamides and prostaglandins are superior to timolol in their ability to lower IOP in glaucoma and OHT patients. In particular, bimatoprost helps more patients achieve low target pressures than timolol and latanoprost do. Latanoprost and travoprost are comparable to each other in IOP-lowering effectiveness and brimonidine is comparable to timolol (without the drug interaction problem with systemic beta-blockers). Coleman's data suggest that the combination drug timolol/dorzolamide is no more effective than bimatoprost, and the two classes of drugs from which it is derived have the longest list of potential side effects of all currently used drugs (personal communication).

From all of these choices, a reasonable initial approach would be to choose a monotherapy that will get the IOP as low as safely possible in each particular patient. Each patient must then be monitored routinely to ensure that IOP is maintained at a level low enough to prevent glaucomatous progression. If a patient's initial therapy fails to reduce IOP to the targeted range, or the visual field is still deteriorating despite a low IOP, it is possible that a different monotherapy may lower IOP more effectively.

Even when using one of the powerful IOP-lowering medications currently available, some patients may need additional IOP lowering in order to prevent disease progression. In such cases, it is best to add an adjunctive drug with a different mechanism

of action than the primary drug, in order to hit another therapeutic target. For example, if the primary drug works by increasing uveoscleral output, such as latanoprost, a drug that decreases aqueous humor production, such as brimonidine, is a good adjunctive choice[33,60] (Fig. 4). A beta-blocker may also be chosen if there are no contraindications present. Similarly, if the primary drug works by increasing outflow through the trabecular meshwork, as does bimatoprost, it is best to choose an adjunctive drug that increases uveoscleral output or that decreases aqueous humor production.

With no way to reverse glaucomatous visual field loss, we must prevent glaucomatous damage with an aggressive approach to lowering IOP. The clinician should use the least amount of medicine that will achieve the maximum IOP-lowering efficacy with minimal adverse effects, starting with or switching to the most powerful single agent that meets the patient's therapeutic requirements. Multiple drugs can increase adverse effects and lead to compliance problems; therefore, there is no rationale for combining multiple low potency medications if a single drug works as effectively. If an adjunctive agent is needed, one with minimal safety concerns and a different mechanism of action is the best choice. The preponderance of scientific evidence supports the superiority of prostaglandins and prostamides as first-line medication for glaucoma patients.

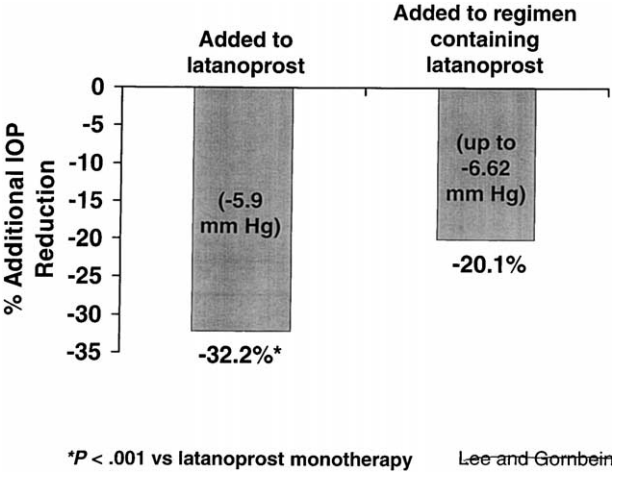



*Fig. 4.* Substantial additional IOP-lowering seen when brimonidine 0.2% added to latanoprost monotherapy or to multi-drug regimens containing latanoprost. In a large, open-label trial of 552 patients, brimonidine was added to multi-drug combinations that included latanoprost in a subset of 56 patients. Brimonidine induced a 32.2% decrease in IOP in patients previously treated with latanoprost only (n = 16). Used adjunctively in patients on a regimen containing latanoprost, a nonselective beta-blocker and dorzolamide, brimonidine induced an additional 20.1% decrease in IOP (n = 11). (This figure was derived from data from Lee and Gornbein.[33])

## Method of Literature Search

The National Library of Medicine database was searched in April 2002 using the PubMed engine (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). All available years were included. Keywords used in the search: *glaucoma, ocular hypertension, intraocular pressure, timolol, adrenergic beta-antagonists, travoprost, latanoprost, bimatoprost, dorzolamide, carbonic anhydrase inhibitors, and compliance.* The most relevant, recent, and rigorous studies were chosen to summarize in this review article. The need to keep this review general and brief rather than in-depth and comprehensive required the literature review to be limited rather than exhaustive. It is inevitable in such a case that some subjective criteria may also creep into the decision making process, so every conscious effort was made to be fair.

## References

1. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. Am J Ophthalmol 132:311–20, 2001
2. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 130:429–40, 2000
3. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmology 105:1146–64, 1998
4. Acheampong AA, Small D, Baumgarten V, et al: Formulation effects on ocular absorption of brimonidine in rabbit eyes. J Ocul Pharmacol Ther 18:325–37, 2002
5. Alm A, Camras CB, Watson PG: Phase III latanoprost studies in Scandinavia, the United Kingdom and the United States. Surv Ophthalmol 41(Suppl 2):S105–10, 1997
6. Asrani S, Zeimer R, Wilensky J, et al: Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 9:134–42, 2000
7. Blackwell B: Drug therapy: patient compliance. N Engl J Med 289:249–52, 1973
8. Bloch S, Rosenthal AR, Friedman L, Caldarolla P: Patient compliance in glaucoma. Br J Ophthalmol 61:531–4, 1977
9. Brandt JD, Wittpenn JR, Katz LJ, et al: Conjunctival impression cytology in patients with glaucoma using long-term topical medication. Am J Ophthalmol 112:297–301, 1991
10. Brubaker RF: Targeting outflow facility in glaucoma management. Surv Ophthalmol 48(Suppl 1): S17–20, 2003
11. Brubaker RF: Mechanism of action of bimatoprost (Lumigan). Surv Ophthalmol 45(Suppl 4):S347–51, 2001
12. Camras CB, Alm A, Watson P, Stjernschantz J: Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. Ophthalmology 103:1916–24, 1996
13. Cantor L: Rating the efficacy, safety and tolerability of topical glaucoma medications. Rev Ophthalmol 9:14–21, 2001
14. Cantor LB: The evolving pharmacotherapeutic profile of brimonidine, an alpha 2- adrenergic agonist, after four years of continuous use. Expert Opin Pharmacother 1:815–34, 2000
15. Carlsen J, Durcan J, Zabriskie N, et al: Nephrolithiasis with dorzolamide. Arch Ophthalmol 117:1087–8, 1999
16. Chandler PA: Progress in the treatment of glaucoma in my lifetime. Surv Ophthalmol 21:412–28, 1977
17. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA:

A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. Ophthalmology 105:1952–9, 1998
18. DuBiner H, Cooke D, Dirks M: Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. Surv Ophthalmol 45(Suppl 4): S353–60, 2001
19. Easthope SE, Perry CM: Topical bimatoprost: a review of its use in open-angle glaucoma and ocular hypertension. Drugs Aging 19:231–48, 2002
20. Eisenberg D, Toris CB, Camras CB: Bimatoprost and travoprost: a review of recent studies of two new glaucoma drugs. Surv Ophthalmol(Suppl 1):S105–15, 2002
21. Epstein R, Brown SV, Dennis RF, Konowal-Allen A: Combination of systemic acetazolamide and topical dorzolamide. Ophthalmology 105:1581–2, 1998
22. Gandolfi S, Simmons ST, Sturm R, et al: Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther 18:110–21, 2001
23. Goldberg I: Relationship between intraocular pressure and preservation of visual field in glaucoma. Surv Ophthalmol 48(Suppl 1): S3–7, 2003
24. Gurwitz JH, Glynn RJ, Monane M, et al: Treatment for glaucoma: adherence by the elderly. Am J Public Health 83:711–6, 1993
25. Hedman K, Alm A: A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. Eur J Ophthalmol 10:95–104, 2000
26. Higginbotham EJ, Schuman JS, Goldberg I, et al: One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. Arch Ophthalmol 120: 1286–93, 2002
27. Kass MA, Heuer DK, Higginbotham EJ: The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 120:701–13, 2002
28. Katz LJ: Twelve-month evaluation of brimonidine-purite versus brimonidine in patients with glaucoma or ocular hypertension. J Glaucoma 11:119–26, 2002
29. Katz LJ: Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine Study Group. Am J Ophthalmol 127:20–6, 1999
30. Kolker AE: Frequency of contraindications to topical betablockers in a glaucoma population [abstract]. Invest Ophthalmol Vis Sci 40(Suppl):S514, 1999
31. Konowal A, Morrison JC, Brown SV, et al: Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol 127:403–6, 1999
32. Lass JH, Khosrof SA, Laurence JK, et al: A double-masked, randomized, 1-year study comparing the corneal effects of dorzolamide, timolol, and betaxolol. Dorzolamide Corneal Effects Study Group. Arch Ophthalmol 116:1003–10, 1998
33. Lee DA, Gornbein JA: Effectiveness and safety of brimonidine as adjunctive therapy for patients with elevated intraocular pressure in a large, open-label community trial. J Glaucoma 10:220–6, 2001
34. Lee ME: Beta adrenergic blocking agents for open-angle glaucoma. J Am Optom Assoc 59:567–71, 1988
35. Lin LL, Galin MA, Obstbaum SA, Katz I: Longterm timolol therapy. Surv Ophthalmol 23:377–80, 1979
36. MacKean JM, Elkington AR: Compliance with treatment of patients with chronic open-angle glaucoma. Br J Ophthalmol 67:46–9, 1983
37. Netland PA, Landry T, Sullivan EK, et al: Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 132: 472–84, 2001
38. Neufeld AH, Bartels SP, Liu JH: Laboratory and clinical studies on the mechanism of action of timolol. Surv Ophthalmol 28(Suppl):286–92, 1983
39. Noecker R, Dirks M, Choplin N: A six-month randomized clinical trial comparing the IOP lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. The Bimatoprost/Latanoprost Study Group. Am J Ophthalmol 135:55–63, 2003
40. Nuzzi R, Finazzo C, Cerruti A: Adverse effects of topical antiglaucomatous medications on the conjunctiva and the lachrymal (Brit. Engl) response. Int Ophthalmol 22:31–5, 1998
41. Olateju SO, Ajayi AA: The lack of efficacy of topical betablockers, timolol and betaxolol on intraocular pressure in Nigerian healthy volunteers. Eye 13:758–63, 1999
42. Orzalesi N, Rossetti L, Invernizzi T, et al: Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. Invest Ophthalmol Vis Sci 41:2566–73, 2000
43. Peak AS, Sutton BM: Systemic adverse effects associated with topically applied latanoprost. Ann Pharmacother 32:504–5, 1998
44. Rosenberg LF, Krupin T, Tang LQ: Combination of systemic acetazolamide and topical dorzolamide in reducing intraocular pressure and aqueous humor formation. Ophthalmology 105:88–92, 1998
45. Rusk C, Sharpe E, Laurence J, et al: Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. Dorzolamide Comparison Study Group. Clin Ther 20:454–66, 1998
46. Schuman JS: Effects of systemic beta-blocker therapy on the efficacy and safety of topical brimonidine and timolol. Brimonidine Study Groups 1 and 2. Ophthalmology 107:1171–7, 2000
47. Schuman JS: Effects of systemic beta-blocker therapy on the efficacy and safety of topical brimonidine and timolol. J Amer Acad Ophthalmol 107:1171–7, 2000
48. Schuman JS: Antiglaucoma medications: a review of safety and tolerability issues related to their use. Clin Ther 22:167–208, 2000
49. Schuman JS, Horwitz B, Choplin NT, et al: A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol 115: 847–52, 1997
50. Shaffer RN: The centennial history of glaucoma (1896–1996). American Academy of Ophthalmology. Ophthalmology 103:S40–50, 1996
51. Sharif NA, Davis TL, Williams GW: [3H]AL-5848 ([3H] 9beta-(+)-Fluprostenol). Carboxylic acid of travoprost (AL-6221), a novel FP prostaglandin to study the pharmacology and autoradiographic localization of the FP receptor. J Pharm Pharmacol 51:685–94, 1999
52. Sherwood M, Brandt J: Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. Surv Ophthalmol 45(Suppl 4):S361–8, 2001
53. Singh K, Spaeth G, Zimmerman T, Minckler D: Target pressure—glaucomatologists holey grail. Ophthalmology 107: 629–30, 2000
54. Sommer A, Tielsch JM, Katz J, et al: Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 109:1090–5, 1991
55. Strahlman E, Tipping R, Vogel R: A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. Arch Ophthalmol 113:1009–16, 1995
56. Tielsch JM, Sommer A, Witt K, et al: Blindness and visual impairment in an American urban population. The Baltimore Eye Survey. Arch Ophthalmol 108:286–90, 1990
57. Toris CB, Camras CB, Yablonski ME, Brubaker RF: Effects of exogenous prostaglandins on aqueous humor dynamics and blood- aqueous barrier function. Surv Ophthalmol 41(Suppl 2): S69–75, 1997
58. Toris CB, Gleason ML, Camras CB, Yablonski ME: Effects of brimonidine on aqueous humor dynamics in human eyes. Arch Ophthalmol 113:1514–7, 1995

59. Van Buskirk EM, Fraunfelder FT: Ocular beta-blockers and systemic effects. Am J Ophthalmol 98:623–4, 1984
60. Walters T, Shapiro A, Chapin M: A comparison of the efficacy, safety, and quality of life of brimonidine with latanoprost vs timolol with latanoprost. Invest Ophthalmol Vis Sci 41:S514, 2000
61. Watson P, Stjernschantz J: A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. Ophthalmology 103:126–37, 1996
62. Weston BC: Migraine headache associated with latanoprost. Arch Ophthalmol 119:300–1, 2001
63. Wheeler LA, Gil DW, WoldeMussie E: Role of alpha-2 adrenergic receptors in neuroprotection and glaucoma. Surv Ophthalmol 45(Suppl 3):S290–4; discussion S295–6, 2001
64. WoldeMussie E, Ruiz G, Wijono M, Wheeler LA: Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. Invest Ophthalmol Vis Sci 42:2849–55, 2001

---

The author reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. The author has received research support from Allergan, Alcon, Pharmacia, and Merck, and he has received honoraria from Allergan and Alcon.

Reprint address: Louis Cantor, MD, Department of Ophthalmology, Indiana University School of Medicine, 702 Rotary Circle, Indianapolis, Indiana 46202.