

## IN THIS ISSUE:

### SPECIAL FEATURE

#### 1 Medical Management of Glaucoma

R. A. Hitchings

### UPDATE

#### 5 IOP-lowering Agents: Mechanisms of Action

Richard F. Brubaker, MD

### CLINICAL FOCUS

#### 7 Compliance

Michael A. Kass, MD

### IN PRACTICE

#### 8 Eye Drop Application

Daniel E. Grigera, MD

### TARGET AUDIENCE

This educational activity is intended for general ophthalmologists, glaucoma specialists, and resident ophthalmologists.

### LEARNING OBJECTIVES

- Discuss the agents available for lowering intraocular pressure (IOP) in glaucoma
- List the drug classes used to lower IOP
- Name the pathways by which aqueous humor can flow out of the anterior chamber
- State three ways to improve patient compliance with topical glaucoma medication regimens
- Describe a technique for topical drop application in patients who are unable to sit up

### EDITORS

Clive Migdal, MD, FRCS, FRCOphth  
Western Eye Hospital, London, UK

George A. Cioffi, MD  
Devers Eye Institute,  
Portland, OR, USA

Ivan Goldberg, MB, FRANZCO, FRACS  
Sydney Eye Hospital, Sydney, NSW,  
Australia

GLAUCOMA TOPICS & TRENDS is published quarterly by Ethis Communications, Inc. and the University of Florida School of Medicine. This publication is administered by an independent editorial board and supported by an unrestricted educational grant from Allergan, Inc.

Copyright 2006 Ethis Communications, Inc. All rights reserved. Neither the University of Florida nor Ethis Communications, Inc. assume any responsibility for injury or damage to persons or property arising from the use of information or ideas contained in this publication.

### COURSE DIRECTOR

Subir Bhatia, MD  
University of Florida, Gainesville, FL, USA

### COURSE REVIEWER

M. Fran Smith, MD  
University of Florida, Gainesville, FL, USA



# GLAUCOMA TOPICS & TRENDS

A CONTINUING MEDICAL EDUCATION PUBLICATION

QUARTER 2 • 2006 • ISSUE 2

## MEDICAL MANAGEMENT

### SPECIAL FEATURE

# Medical Management of Glaucoma

R. A. Hitchings

**The term glaucoma comprises a group of mainly chronic conditions that is characterized by progressive deformation of the optic nerve head and for which elevated intraocular pressure (IOP) is a risk factor. Affecting primarily the middle aged and elderly, the glaucomas currently constitute the second most common cause of treatable blindness worldwide.<sup>1-3</sup> In most of the world, the initial and typically the most effective treatment is topically applied hypotensive medication, whether or not the baseline IOP is above the upper limit of normal.<sup>4</sup>**

In reviewing the medical management of glaucoma, this article will look at the classification, combinations, and side effects of today's hypotensive drugs. Then it will review first-line and secondary therapy, target pressures, and IOP fluctuation. Briefly, it will look at compliance, cost, and quality of life issues. These subjects are also well covered in the glaucoma treatment guidelines of the European Glaucoma Society (EGS) and the South East Asia Glaucoma Interest Group (SEAGIG).<sup>5,6</sup>

### Drug Classes and Combinations

There are five classes of topical hypotensive medication: prostaglandins and prostamides (together referred to as "prosta" agents), beta-blockers, selective (alpha-2) adrenergic agonists, carbonic anhydrase inhibitors (CAIs), and cholinergics (Table I). It should be remembered that the efficacy of these agents can vary enormously from patient to patient (Table II).

In theory, an agent from any one of the ma-

inor drug classes could be combined in one container with a drug from another class, increasing the hypotensive effect without adding to the patient's inconvenience. In practice, patent and formulation issues have limited the number of combination therapies on the market (Table III). Combining two agents in a single bottle should improve compliance and spare the conjunctiva exposure to extra preservative.<sup>7,8</sup>

However, combinations do not always achieve the hypotensive effect of the preparations given separately. For example, the addition of timolol to latanoprost achieved only a 1-1.5 mm Hg additional reduction in IOP. This was less than expected, although this finding has recently been disputed.<sup>8-12</sup>

**TABLE I** Expected IOP Reduction by Class of Topical Hypotensive Agent

Group	Peak change (mm Hg)***	Relative change (%)
Prosta drugs*	8.4	33
Beta-blockers**		
Selective	6.0	23
Non-selective	6.9	29
Alpha-adrenergics	6.1	25
Topical CAIs	5.9	22

\* "Prosta" drugs include prostamides and prostaglandins. Prostamides have a small additional IOP reduction over the prostamides.<sup>43</sup>

\*\* Non-selective beta-blockers in are represented by timolol<sup>5</sup>

\*\*\* 24-hour IOP change may show a fluctuation between 1-2 mm Hg

Source: Modified from Van der Valk and coworkers<sup>43</sup> Table 4.

### Side Effects

All the topical hypotensives are powerful chemical agents and can have significant local and systemic side effects (Table IV). Within a

# GLAUCOMA TOPICS & TRENDS

**STATEMENT OF NEED AND PROGRAM DESCRIPTION** Recent months and years have seen significant advances in our understanding of glaucoma. Much has been learned, not only about damage mechanisms and pathogenesis, but also about diagnosis and management. Treatment options—both medical and surgical—continue to expand. This program will review this new knowledge with an emphasis on incorporating recent insights into day-to-day practice.

**GENERAL INFORMATION** In order to receive CME credit, participants should read the report, and then go to our online test engine at: <http://cme.ufl.edu/selfstudy/glau/> After completing the posttest, a score of 70% is required to qualify for CME credit. You will be able to print your certificate at the completion of the posttest. There is no fee to participate in this activity. Estimated time to complete the activity is 60 minutes.

**DATE OF ORIGINAL RELEASE** June 2006. Approved for a period of 12 months.

**ACCREDITATION STATEMENT** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Florida College of Medicine and Ethis Communications, Inc. The University of Florida College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

**CREDIT DESIGNATION STATEMENT** The University of Florida College of Medicine designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**DISCLAIMER** Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and professional development. The information presented in this activity is not meant to serve as a guideline for patient care. Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, applicable manufacturer's product information, and comparison with recommendations of other authorities.

**COMMERCIAL SUPPORTERS** This activity is supported by an educational grant from Allergan, Inc.

## FACULTY AND DISCLOSURE STATEMENTS

**R.A. HITCHINGS, MD**, is a professor of glaucoma and allied studies, University College London, and a consultant ophthalmologist at Moorfields Eye Hospital, London, UK. Dr. Hitchings states that he is not an employee of, consultant to, or holder of any financial or proprietary interest in any product discussed in his article. Within the past 5 years he has been a consultant to and/or received funding from Alcon, Allergan, and Santen.

**MICHAEL A. KASS, MD**, is professor and chair, department of ophthalmology and visual science, Washington University School of Medicine, St. Louis, MO. Dr. Kass states that he is not an employee of, consultant to, or holder of any financial or proprietary interest in any product discussed in his article. Within the past 5 years he has been a consultant to and/or received support from Alcon, Allergan, Merck, and Pfizer.

**RICHARD F. BRUBAKER, MD**, is professor of ophthalmology emeritus, Mayo Clinic, Rochester, MN. Dr. Brubaker states that he is not an employee of, consultant to, or holder of any financial or proprietary interest in any product discussed in his article. Within the past 5 years he has been a consultant to and received compensation from Allergan and Merck.

**DANIEL E. GRIGERA, MD**, is assistant professor of ophthalmology, Universidad del Salvador, and head of the glaucoma service, Hospital Oftalmológico Santa Lucia, Buenos Aires, Argentina. Dr. Grigera states that within the past 5 years he has not been a consultant to or received support from any medical or pharmaceutical company.

## SPECIAL FEATURE

class, local and systemic responses may differ. For example, conjunctival hyperemia appears to be greater with the prostamide bimatoprost than with the prostaglandin latanoprost, and the selective beta-blocker betaxolol has fewer respiratory side effects than the nonselective beta-blocker timolol.<sup>13-15</sup>

As no safety studies have been performed on children, ocular hypotensive drugs must be used with caution in pediatric cases. Both phy-

time, topical beta-blockers became the glaucoma drugs of choice worldwide; however, experience with these drugs revealed their systemic side effects.<sup>16-19</sup>

The Ocular Hypertension Treatment Study (OHTS) took place during the introduction of the prosta agents, and drug usage over the course of the study demonstrated a gradual replacement of beta-blockers by prosta drugs, which offer once-a-day use, better IOP reduction, and few local (and negligible systemic)

**TABLE II Drug Mechanism and Duration of Action**

Class	Mechanism	Onset (hours)	Peak (hours)	Duration (hours)	Washout
Alpha-2 agonists	Aq. secretion reduced Trabecular outflow increased	1-2 4-6	4-5	12	1-3wks
Beta-blockers*	Aq. secretion reduced	2	2-3	12	2-5wks
CAIs**	Aq. secretion reduced	1-2	6-8		7 days
Cholinergics***	Trabecular outflow increased	1	6-7		3 days
Prostaglandins/ Prostamides	U/V outflow increased	2-4	8-12	24+	4-6 wks

\* Beta-blockers with or without intrinsic sympathomimetic activity (ISA). ISA has no proven additional benefit  
 \*\* CAIs may be topical or systemic. Systemic use is restricted to special situations rather than for routine use.  
 \*\*\* Cholinergics such as pilocarpine gel are given just at night, with an effect lasting 20-24 hours. Ocuserets (pledgets) are given weekly. Pilocarpine and its derivatives are "direct acting" cholinergics and are reversible in action. "Irreversible" cholinergics have no place in glaucoma practice.

(Adapted from the EGS guidelines)

sician and parent need to understand the possibility of magnified side effects. The use of alpha-2 agonists is contraindicated in the young.

side effects.<sup>20</sup> This pattern of use has been picked up by general ophthalmologists in North America. Elsewhere, however, beta-blockers re-

**TABLE III Available Drug Combinations**

First Line	Additional Drug				
	Prostas	Beta-blockers	Alpha-2 agonists	CAIs	Cholinergics
Prostas	X	Yes*	No	No	No
Beta-blockers	Yes*	X	Yes**	Yes***	Yes****
A-2 agonists	No	Yes***	X	No	No
Topical CAIs	No	Yes***	No	X	No
Cholinergics	No	Yes****	No	No	X

### DISTRIBUTION

\* Latanoprost 0.005% and timolol 0.5% (Xalcom/Xalacom; Worldwide)  
 \*\* Brimonidine 0.2% and timolol 0.5% (Combigan; EU, Canada, Australasia)  
 \*\*\* Timolol 0.5% and dorzolamide 2% (Cosopt; Worldwide)  
 \*\*\*\* Carteolol 2% and pilocarpine 1% (CarPilo; EU)  
 \*\*\*\*\* Timolol 0.5% and pilocarpine 1-4% (Timpilo, Fotil, Equiton, Timicon; EU)  
 \*\*\*\*\* Metipranolol 0.1% and Pilocarpine 2% (Ripix, Normaron; EU)

## First-line and Secondary Therapies

Before the advent of the beta-blocker timolol, most topical hypotensives had to be instilled three or more times a day and had significant local side effects. Timolol was a landmark drug because of its twice-daily dosage and good ocular tolerability. In

main the most widely prescribed antiglaucoma drugs (Figure 1).

Reasons for the predominance of topical beta-blockers include familiarity with the drug class plus local cost pressures that inhibit use of first-choice agents by restricting first-line use. A first-choice agent is the drug chosen on medical grounds, whereas a first-line

**TABLE IV** Local and Systemic Side Effects of Topically Applied Drugs

	Prostas	Beta-blockers	Alpha-2 adrenergics	Topical CAIs	Cholinergics	Non-selective adrenergics
<b>Local side effects</b>						
Conjunctival hyperemia	1-3+	0-1+	1-3+	1-3+	1-3+	0-4+
Topical allergies	0-3+	0-1+	1-3+	0-1+	01-+	0-4+
Hypertrichosis	1-3+	0	0	0	0	0
Eyelid darkening	1-3+	0	0	0	0	0
Iris pigmentation	1-3+	0	0	0	0	0
Uveitis	1-3+	0	0	0	0	0
CME	1-3+	0	0	0	0	0
Corneal edema	0	0	0	0-1+	0	0
Recurrence HSV keratitis	0-1+	0	0	0	0	1-2+
Miosis, headache	0	0	0	0	1-3+	0
<b>Systemic side-effects</b>						
Bradycardia/hypotension	0	1-3+	0	0	0	0
Tachycardia/hypertension	0	0	0	0	0	0-2+
Bronchospasm	0	0-4+	0	0	0-3+	0
Drowsiness and lethargy	0	0-2+	2-3+	0	0	0
Elevated serum lipids	0	2-3+	0	0	0	0
<b>Tolerability</b>						
	2-4+	3-4+	2+	1-4+	2-3+	2-3+
<b>Daily dosage frequency</b>						
	1	1+	1-2+	3-4+	3-4+	2-3+

agent is selected on non-medical (usually cost) grounds. The introduction of the prosta drugs in New Zealand and Australia was followed by instructions in the former that they could only be used after a trial of topical CAIs, and in the latter they could be used only “after other agents had failed.” These restrictions have now been lifted.

Some European countries, including Italy, have recently introduced restrictions whereby generic timolol is to be used, and patients may be switched to prosta drugs only if timolol is found inadequate. Similar restrictions exist in Scotland. In Germany repay-

a second drug or to switch to a different single agent. There is no simple approach, but the following suggestions may apply:

- If the first drug has had an effect no greater than normal fluctuation, it can be deemed ineffective. Thus, it would be reasonable to switch to another class of drug.
- If the first drug had too small a hypotensive effect and another class of drug would be likely to achieve the desired IOP reduction, switch to an alternative monotherapy.
- If the first drug had a hypotensive effect within its expected range but that effect was still inadequate, then add a second drug.

As single drops are preferred by the patient (and improve compliance), use combination preparations if the expected additional IOP reduction will deliver the needed IOP control. If not, add a second bottle.

With all additions, consideration needs to be given to the risk of additional side effects, reduction in compliance, and the inevitable risk/benefit profile—ie, whether the addition will have a material effect on the patient’s known or presumed rate of visual loss. In younger patients, more aggressive therapy can be justified to halt a possibly slow rate of disease progression; in elderly patients such an aggressive approach to a very slow rate of vision loss may not be needed.

### Target Pressure

Target pressure is an IOP range that minimizes the risk of (further) visual loss.<sup>21-23</sup> With medical therapy, IOP is unlikely to become

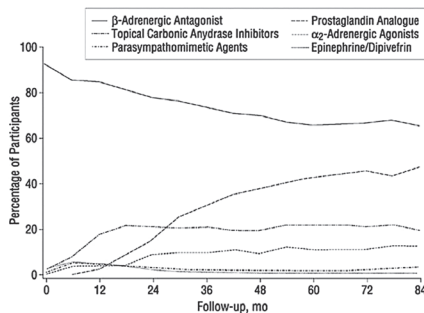
## Core Concepts

- The initial, and typically the most effective, treatment for glaucoma is pharmacologic IOP reduction
- IOP-lowering agents in different classes act by different mechanisms
- Adding a second or third IOP-lowering drug produces significantly less IOP reduction than the sum of the IOP reductions of the agents given separately
- Combining drugs from different IOP-lowering classes in a single drop increases compliance
- Target IOP is an IOP range that minimizes the risk of further visual loss; 18 mm Hg is a common target IOP
- With high initial IOPs, the target IOP may not be achievable with medical therapy alone
- Treatment should aim to flatten the diurnal IOP fluctuation curve as well as control long-term pressure fluctuations
- Cost, convenience, compliance, and quality of life issues impact drug selection

dangerously low, so the target pressure can be set as an upper IOP limit. Analysis of results from the Advanced Glaucoma Intervention Study (AGIS) showed (in the associative analysis) that least progression occurred when all IOP measurements were 18 mm Hg or below.<sup>24</sup> This seems a sensible level at which to start setting target pressures for chronic glaucoma. (Such a level may be inappropriate for the management of ocular hypertension, however.)

What sort of IOP reduction is needed to achieve this target will depend on the baseline IOP. This can be seen in Figure 2, which has been modified from the EGS guidelines.

When a patient’s baseline IOP exceeds 30 mm Hg, the percentage IOP reduction needed to achieve an 18 mm Hg target IOP will likely to require more than one agent. In the case of normal-tension glaucoma (NTG), at least a 25% reduction in IOP is needed. If an NTG patient starts with a baseline IOP of 17 mm Hg, then a reduc-



Reprinted with permission Kass, M. A. et al. Arch Ophthalmol 2002; 120:701-713.  
**FIGURE 1.** Drug usage as unit sales world-wide. (Reproduced with permission.)

ment options available to the ophthalmologist restrict primary use to non-prosta drugs.

### Add or Switch?

Where the first-choice or first-line drug is unable to achieve the identified target IOP, a decision on a second-line treatment must be selected.<sup>21-23</sup> The options are to add

tion of 4 mm Hg would be required.<sup>25,26</sup> The Collaborative Normal Tension Glaucoma Study (CNTGS) demonstrated that a 30% reduction could be achieved by medical means only 50% of the time.<sup>21</sup> Even with the advent of prosta drugs (which were not available during the CNTGS), a 30% reduction will require surgery in a significant proportion of cases.

## Fluctuation

Recent studies have thrown some light on the effect of sleep and postural change on IOP. IOP peaks just before waking, at a time when systolic blood pressure could be reduced.<sup>27</sup> Such IOP changes are not due to circadian changes in central corneal thickness, which alters little over the 24 hours.<sup>28</sup> Although no direct causal link has been detected, the coincidence of nocturnal IOP spikes with nocturnal dips in blood pressure would affect perfusion pressure, and reduced perfusion pressure has been associated with a higher incidence of glaucoma in the gen-

sure as well, it should be used with caution (or in combination) in those patients where blood pressure lability and ocular perfusion could be in doubt.

## Compliance

A recent review concluded that poor compliance was common in glaucoma patients, although it could not link this with progression of visual loss.<sup>32</sup> A study using dropper bottles that timed the application of medication showed how irregularly patients instilling drops three to four times a day were compared to those who used drops twice a day.<sup>33</sup>

It has been found that compliance improves with better communication with the patient, and with single rather than multiple bottles.<sup>7,34,35</sup> In addition, several recent studies have demonstrated that patients continue taking drugs administered once (rather than twice) a day for a longer period (ie, patients exhibit greater “persistency”).<sup>36,37</sup> These results suggest that medical treatment be restricted to as few bottles as possible and medications should be administered once or twice a day.

## Cost Issues

As has been noted, local cost issues have caused restrictions on first-line use of prosta drugs. Currently, timolol, which is available as a generic agent, is relatively inexpensive; the prosta drugs are more expensive. For patients in poorer countries, cost issues (often combined with poor compliance and poor persistence) can limit the value of medical therapy. This has led to the testing of “early” and, in some cases, primary surgery. Trials of this approach have proven successful<sup>38</sup> especially when cheap

anti-fibrotic agents are used (eg, 5-fluorouracil) or beta-irradiation.<sup>39</sup>

## Quality of Life Issues

The diagnosis of chronic glaucoma has been linked to significant mood changes, because of the perception that glaucoma is an untreatable condition leading to inevitably blindness and other visual symptoms.<sup>40,41</sup> Once the diagnosis has been made good communication can reduce these anxieties.<sup>41</sup> Treatment-related side effects will also reduce health-related quality of life scores.<sup>42</sup>

## Conclusion

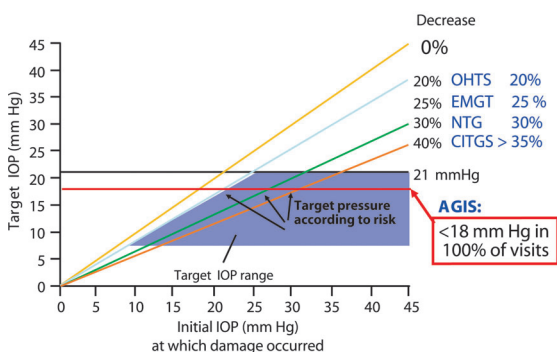
The advent of more powerful topical hypotensives that require fewer drops per day and have fewer side effects has led to better patient compliance and better control of IOP in most of the chronic glaucomas. Better understanding of patient quality of life issues combined with enhanced medical therapy should lead to better long-term visual outcomes for glaucoma patients diagnosed today than was possible for patients diagnosed two decades ago. ●

*R.A. Hitchings is a professor of glaucoma and allied studies, University College London, and a consultant ophthalmologist at Moorfields Eye Hospital, London, UK.*

## REFERENCES

1. Quigley HA: Proportion of those with open-angle glaucoma who become blind. *Ophthalmology* 1999;106:2039-41.
2. Garway-Heath DF, Rudnicka AR, Lowe T, et al: Measurement of optic disc size: equivalence of methods to correct for ocular magnification. *Br J Ophthalmol* 1998;82:643-9.
3. Thylefors B, Negrel AD: The global impact of glaucoma. *Bull World Health Organ* 1994;72:323-6.
4. Maier P, Funk J, Schwarzer G, et al: Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *Brit Med J* 2005;331:134.
5. European Glaucoma Society: Terminology and Guidelines for Glaucoma. Ed 2. Published by the European Glaucoma Society, 2004.
6. South East Asia Glaucoma Interest Group: Asia Pacific Glaucoma Guidelines. Published by South East Asia Glaucoma Interest Group, Singapore, 2004.
7. Diestelhorst M, Nordmann JP, Toris CB: Combined therapy of pilocarpine or latanoprost with timolol versus latanoprost monotherapy. *Surv Ophthalmol* 2002;47(suppl 1):155-61.
8. Fechtner RD, Realini T: Fixed combinations of topical glaucoma medications. *Curr Opin Ophthalmol* 2004;15:132-5.
9. Rulo AH, Greve EL, Hoyng PF: Additive effect of latanoprost, a prostaglandin F2 alpha analogue, and timolol in patients with elevated intraocular pressure. *Br J Ophthalmol* 1994;78:899-902.
10. Racz P, Ruzsonyi MR, Nagy ZT: Around-the-clock intraocular pressure reduction with once-daily application of latanoprost by itself or in combination with timolol. *Arch Ophthalmol* 1996;114:268-73.
11. Higginbotham EJ, Feldman R, Stiles M, Dubiner H: Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol* 2002;120:915-22.
12. Diestelhorst M, Larsson LI: A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology* 2006;113:70-6.
13. Parrish RK, Palmberg P, Sheu WP: A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol* 2003;135:688-703.

Additional references for this article can be found on [www.GlaucomaTopics.com](http://www.GlaucomaTopics.com)



**FIGURE 2. Target pressure.** The percentage IOP reduction achieved in the recent major clinical trials is shown against the reduction needed to achieve a target pressure of 18 mm Hg. (Note that the % and absolute IOP reduction required to achieve these target pressures will in most instances lie outside the expected effect of monotherapy in cases where the base line IOP is greater than approximately 27 mm Hg.) Adapted from the EGS guidelines with permission.

eral population and a greater risk of progression in timolol-treated eyes.<sup>29,30</sup>

It is theoretically possible that nocturnal pressure spikes, acting either directly or indirectly, by reducing ocular perfusion pressure also hasten progression of visual field loss in glaucoma. Because of this possibility, treatment should aim to flatten the diurnal curve as well as control long-term fluctuation. Orzalezi compared the ability of three drugs, timolol, brimonidine and latanoprost, to do this.<sup>31</sup> He found that timolol failed to control nighttime IOP as well as the other two. As timolol may lower systemic blood pres-

# IOP-lowering Agents: Mechanisms of Action

Richard F. Brubaker, MD

Ocular hypotensive drugs are the backbone glaucoma therapy. These drugs are typically classified as either aqueous humor secretory suppressors or aqueous humor outflow enhancers. Although their most important therapeutic property is that they lower intraocular pressure (IOP), there are subtle differences in their effects and mechanisms of action (Figure 1).

Three classes of drug can inhibit aqueous humor formation: suppressors of adrenergic beta receptors, activators of adrenergic alpha-2 receptors, and carbonic anhydrase inhibitors.<sup>1</sup> It is likely that all these agents target the nonpigmented ciliary epithelial

the extraocular recipient vessels, and some glaucoma drugs may (to a small extent) act in this manner. Additionally, pressure in the episcleral veins may not tell the whole story, as some aqueous drainage may bypass these vessels.

A second mechanism of action is to enhance the facility of outflow through the major outflow pathway—the trabecular meshwork, Schlemm’s canal, and the collector channels. The older cholinergic drugs (eg, pilocarpine) act on this pathway. In monkey eyes, this effect is completely eliminated by disinsertion of the ciliary muscle.<sup>2</sup> A direct effect on the cells of the trabecular meshwork has been also demonstrated.<sup>3</sup> A consistent finding in glaucomatous eyes with elevated IOP is a reduction in outflow facility as measured by tonography.<sup>4</sup> Thus, drugs that improve outflow facility tend to normalize the aqueous dynamics of the glaucomatous eye.

A third hypothetical mechanism involves the uveoscleral outflow pathway, first described by Anders Bill.<sup>5</sup> Bill injected intracameral tracers and followed their flow from the anterior chamber into the supraciliary space, the potential space between the uvea

and the sclera in the posterior segment of the eye. He found, to his surprise, that a moderate portion of aqueous outflow occurred posteriorly; but, unlike the anterior outflow, the rate of posterior outflow was largely unaffected by IOP.

## Prostaglandin Hypotensives

Clinical interest in the uveoscleral outflow pathway increased with the discovery that the action of prostaglandin ocular hypotensives could not be explained by suppression of aqueous formation or im-

## Core Concepts

- Agents that reduce aqueous humor formation:
  - Suppressors of beta adrenergic receptors
  - Activators of alpha-2 adrenergic receptors
  - Carbonic anhydrase inhibitors
- Aqueous humor suppressors cannot reduce aqueous secretion by more than 50%
- Outflow enhancement mechanisms:
  - Enhance outflow facility
  - Increase uveoscleral outflow
  - Reduce pressure of extraocular recipient vessels
- Prostaglandin agents appear to work by increasing uveoscleral hydraulic conductivity

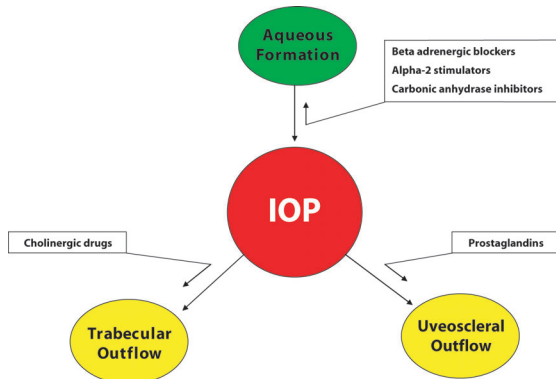


FIGURE 1. Medical approaches to lowering intraocular pressure (IOP).

layer of the pars plicata, the tissue that normally secretes aqueous humor. At most, these agents can reduce daytime aqueous humor secretion by approximately 50%. They have either no effect or a much weaker effect on nocturnal aqueous humor secretion. Since the nocturnal rate of aqueous formation in humans is roughly half the daytime rate, it is as if these drugs put the pars plicata into a chronic state of sleep. No aqueous suppressor can eliminate the baseline 50% rate of secretion.

## Enhancing Outflow

There are, in theory, three means by which improving outflow can lower IOP. The simplest is to reduce the pressure of

provement of outflow facility. In animal eyes, these drugs were found to increase uveoscleral outflow, and that was regarded as sufficient to explain their ocular hypotensive effect.<sup>6</sup> Investigators then focused on the effects of prostaglandin hypotensives on the uveal and scleral tissues and found that these drugs alter the metabolism of tissue remodeling.

For example, it has been shown that in the ciliary muscle, a prostaglandin analog increases transcription of genes that code for metalloproteinases.<sup>7</sup> The resulting increase in synthesis of these degradative en-

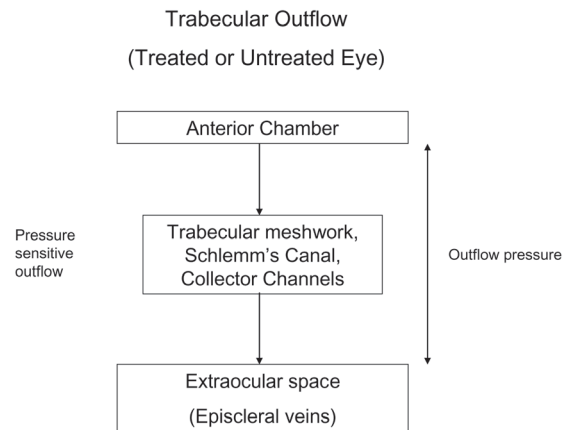


FIGURE 2. Trabecular outflow (treated or untreated eye).

zymes changes the rate of turnover of extracellular matrix molecules and alters the tissues. The result is enhanced hydraulic

conductivity, which is probably the basis for the prostaglandins hypotensive effect.

We would expect that increasing the hydraulic conductivity of uveoscleral outflow tissues would improve the tonographic facility of outflow, and some but not all investigators have reported this effect with the prostaglandins.<sup>8</sup> However, improvement of the tonographic facility cannot account for all or even most of the prostaglandins' effect. One must look deeper

the pressure within the eye. Thus, when pressure rises in the eye, the outflow pressure rises by an equal amount, and the rate of outflow increases (Figure 2). This is the major means by which IOP is kept stable in the normal eye.

### Uveoscleral Outflow

The situation with the uveoscleral outflow pathway is different. Outflow through this pathway is a two-step process. The

fluid must first enter the suprachoroidal space. Second, it must pass either into the choroidal circulation or through the sclera into orbital tissues outside the eye. The first step is the rate-limiting step. Were this not the case, the suprachoroidal space would ordinarily be filled with fluid, which it is not.

The outflow pressure that drives fluid from the anterior chamber into the suprachoroidal space is the difference between the pressures in these two compartments (Figure 3). Since these two compartments are not separated by an inelastic tissue, when IOP changes the outflow pressure for this first step in uveoscleral outflow will not change. This fact may explain how a drug can lower IOP by increasing the hydraulic conductivity of the uvea and sclera without changing the facility of outflow.

A drug may alter the hydraulic conductivity of the uvea to such an extent that the first step of the uveoscleral outflow process is no longer rate-limiting. If so, the outflow pressure for the pathway now becomes the difference between the pressure inside the eye and the tissue pressure

now also be pressure sensitive. Clinical tonography will be able to detect a facility-enhancing effect of the drug.

Tonography, however, cannot localize the drug effect to a particular anatomic site. Thus, when a prostaglandin is found to improve outflow facility, we cannot assume that the effect is due to a change in the trabecular pathway. The drug may have caused the uveoscleral pathway to become pressure sensitive.

The evidence from humans and animals is that prostaglandin-related hypotensive agents increase uveoscleral flow by increasing hydraulic conductivity. The more potent this effect, the more likely that an additional effect, an increase in facility of outflow, will become measurable. Whether these drugs have direct effects on the trabecular outflow pathway that contribute to an increase in facility of outflow remains an important question.

Much remains to be learned. This discussion oversimplifies what is likely a more complicated process.<sup>9</sup> The problem of understanding drug action is even more difficult in the glaucomatous eye where a disease process is superimposed on the pharmacologic actions of the drug. ●

Richard F. Brubaker, MD, is a professor of ophthalmology emeritus, Mayo Clinical, Rochester, MN.

### REFERENCES

1. Brubaker RF: Flow of aqueous in humans. *Invest Ophthalmol Vis Sci* 1991;32:3145-66.
2. Kaufman PL, Bárány EH: Residual pilocarpine effects on outflow facility after ciliary muscle disinsertion in the cynomolgus monkey. *Invest Ophthalmol* 1976;15:558-61.
3. Erickson KA, Schroeder A: Direct effects of muscarinic agents on the outflow pathways in human eyes. *Invest Ophthalmol Vis Sci* 2000;41:1743-8.
4. Grant WM: Tonographic method for measuring the facility and rate of aqueous flow in human eyes. *Arch Ophthalmol* 1950;44:204-14.
5. Bill A: The aqueous humor drainage mechanism in the cynomolgus monkey (*Macaca iris*) with evidence for unconventional routes. *Invest Ophthalmol* 1965; 4: 911-9.
6. Nilsson SF, Samuelsson M, Bill A, Stjernschantz J: Increased uveoscleral outflow as a possible mechanism of ocular hypotension caused by prostaglandin F2 alpha-1-isopropylester in the cynomolgus monkey. *Exp Eye Res* 1989;48:707-16.
7. Weinreb RN, Lindsey JD: Metalloproteinase gene transcription in human ciliary muscle cells with latanoprost. *Invest Ophthalmol Vis Sci* 2002;43:716-22.
8. Alm A, Villumsen J: PhXA34, a new potent ocular hypotensive drug. A study on dose-response relationship and on aqueous humor dynamics in healthy volunteers. *Arch Ophthalmol* 1991;109:1564-8.
9. Becker B, Neufeld AH: Pressure dependence of uveoscleral outflow. *J Glaucoma* 2002;11:545.

### Uveoscleral Outflow (Untreated Eye)

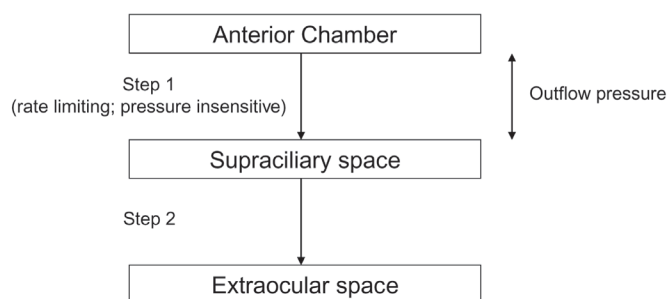


FIGURE 3 Uveoscleral outflow (untreated eye).

into the anatomical differences between the uveoscleral and the trabecular outflow pathways to understand this apparent inconsistency.

The rate of outflow through a tissue is driven by the hydrostatic pressure difference across the tissue and the hydraulic conductivity of that tissue. In the case of the trabecular pathway, that pressure difference, the outflow pressure, is the difference between the IOP and the pressure in

### Uveoscleral Outflow (Treated Eye)

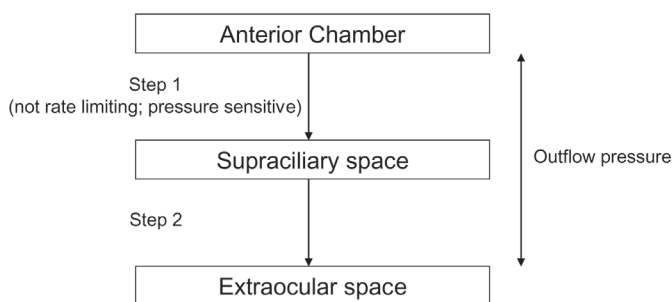


FIGURE 4 Uveoscleral outflow (treated eye).

the veins outside the eye. Because the sclera is inelastic, the pressure in the episcleral veins is almost completely independent of

the pressure within the eye. Thus, when pressure rises in the eye, the outflow pressure rises by an equal amount, and the rate of outflow increases (Figure 2). This is the major means by which IOP is kept stable in the normal eye.

outside the sclera (Figure 4). Just as the trabecular outflow pathway is pressure sensitive, the rate of uveoscleral outflow will

# Compliance

Michael A. Kass, MD

**Poor compliance, defaulting, is a common and frequent cause of treatment failure in glaucoma patients. Various studies indicate that 28-59% of glaucoma patients default from treatment, depending on how compliance is defined and the technique used to measure it.**

Recently, investigators have utilized data from health insurers to study persistence (the time the patient continues taking a medication) and adherence (the number of doses taken at the appropriate time intervals). Nordstrom et al reviewed 5,300 newly treated glaucoma suspects and patients and found that within 6 months, nearly half the patients had discontinued their medication.<sup>1</sup> By 3 years, only 37% were still on the original medication.

## Why Do Patients Default?

Patients may default for many reasons. Tsai and colleagues clustered the reasons for poor compliance into four domains:<sup>2</sup>

- Situational and environmental reasons, eg, lack of social support, difficulty traveling to doctor or pharmacy;
- The medical regimen, eg, complexity of

the regimen in terms of the number of medicines and dosing schedules, side effects, medication costs;

- Patient factors, including the patient's beliefs about the severity of the disease and personal susceptibility, memory, comorbid medical conditions; and
- Provider factors, including the patient-physician relationship and the physician's ability to communicate.

Except in rare cases, it is difficult for physicians to recognize defaulting. When questioned, most patients will tell the doctor what they believe the doctor wants to hear. Electronic monitors have been used to measure compliance, but they are not yet commercially available.<sup>3</sup> A number of questionnaires are reported to be useful in detecting poor compliance, but these have not yet been validated for ophthalmic care. Information about refilling prescriptions is available in some health payment systems and may be useful.

## What Can Be Done?

There are many things physicians and healthcare workers can do to aid patient compliance (Table I). The most important include:

## Core Concepts

- Compliance is a very serious problem in the medical treatment of glaucoma
- Reasons for noncompliance are many and complex
- New tools may become available for monitoring compliance
- Physicians must take steps to improve compliance

- Reducing the complexity of the regimen, eg, by prescribing the smallest number of drugs and the least number of doses per day;
- Improving the patient-physician relationship;
- Regularly teaching patients about the disease and its treatment; and
- Using memory aids that list the drugs, doses, time of administration, and proper technique of administration.

Defaulting from therapy is a common and serious problem. In the future, it is hoped that electronic monitors and data from prescription-refill records will allow physicians to recognize defaulting more readily and to make appropriate interventions or choose alternative forms of therapy, such as laser or incisional surgery. ●

Michael A. Kass, MD, is professor and chairman, department of ophthalmology & visual sciences, Washington University School of Medicine, St. Louis, MO.

## REFERENCES

1. Nordstrom BL, Friedman DS, Mozaffari E, et al: Persistence and adherence with topical glaucoma therapy. *Am J Ophthalmol* 2005;140:598-606.
2. Tsai JC, McClure CA, Ramos SE, et al: Compliance barriers in glaucoma: a systematic classification. *J Glaucoma* 2003;12:393-98.
3. Kass MA, Meltzer DW, Gordon M, et al: Compliance with topical pilocarpine treatment. *Am J Ophthalmol* 1986;101:515-23.

## Pearls for Improving Patient Compliance

- Explain glaucoma, the rationale for treatment, and how drugs act; re-explain on return visits
- Anticipate and explain side effects
- Spend adequate time with the patient
- Have printed cards for medication schedules
- Demonstrate drop administration and observe technique
- Prescribe the minimum number of medications and minimum number of doses
- Tailor dosing schedule to daily events
- When changing regimen, change one medication at a time
- Make patients aware of devices to aid eyedrop administration
- Enlist family members, friends, neighbors
- Ask patients to use medication monitors
- Ask patients to share pharmacy records of refills

For back issues of  
**GLAUCOMA**  
 TOPICS & TRENDS  
 visit  
[www.GlaucomaTopics.com](http://www.GlaucomaTopics.com)

# Eye Drop Application

Daniel E. Grigera, MD

As simple as it is to instill an eyedrop, much can—and frequently does—go wrong. Difficulties with instillation cause at least a quarter of our patients to miss doses.<sup>1</sup> Also, potentially risky techniques, such as touching the eye with the tip of the dispenser, are not uncommon. Drop instillation problems can lead to treatment failure, use of unnecessary additional medication, or infection.<sup>2</sup> Furthermore, systemic absorption may be minimized by an appropriate instillation technique.<sup>3</sup>

## Instillation Technique

Determining beforehand how well the patient or the patient's caregivers can administer eyedrops is of primary importance. Careful instructions on eyedrop instillation should be given to every patient (or caregiver) at the beginning of therapy.

For a patient without physical limitations the conventional technique may be applied:

- Use both hands (previously washed).
- If seated: the head is tilted slightly backwards while gazing upward. The lower lid is gently pulled down with the nondominant hand to form a small concavity in which the drops will be placed. With dominant hand, the dispenser is held above this concavity.
- If lying in bed: maintain both lids open with non-dominant hand, hold the dispenser above the eye with dominant hand, while looking at the tip of the bottle.
- In both cases the bottle should be near enough to make sure that the drop will enter the eye and far enough so as not

to touch it (2-5 cm).

- Avoid blinking and gently press on the body of the bottle so that a single drop falls into the eye.
- After application, lids should be kept closed (or digital compression be applied to the punctum) for 1-2 minutes to minimize systemic absorption.
- Replace bottle cap.
- Carefully wipe the excess from the skin, especially when using medications that may darken skin.
- Ask a relative or caregiver to observe, at least at the beginning, whether the drops fall as they should.

## Patients with Limitations

When patients have memory problems, other psychiatric impairments, severe arthritis, or abnormal movements such as Parkinson disease, a caregiver should be asked to perform the task.



FIGURE 1. The tactile method for locating the drop.

The unaided glaucoma patient with unilateral or bilateral loss of fixation is a frequent cause of concern. Mechanical devices have had only limited success with these patients; however, for patients with adequate dexter-

## Core Concepts

- Determine patient's ability to perform eyedrop instillation.
- Explain instillation technique to patient and relative/caregiver.
- Patients with impaired fixation can try the tactile method.
- Ask patient to demonstrate instillation.

ity and the ability to learn the technique, Ritch and coworkers' tactile method may be a useful tool.<sup>4</sup>

- Pull down the lower lid with the index finger of the nondominant hand. The finger should be bent at the second knuckle at a right angle to serve as a guide for the dominant hand (holding the bottle). The thumb of the dominant hand slides slowly along the index finger, and on reaching the second knuckle, the dispenser is aimed downward. At that moment, the tip is directly above the eye (Figure 1).

## Other Considerations

- When the eyedrop is a suspension, shake the bottle before administration.
- Wait at least 5 minutes between instillation of two different eyedrops.<sup>5</sup>
- When each eye receives a different treatment, labelling should indicate the eye and the interval.
- Asking the patient to demonstrate instillation is useful for correcting mistakes. ●

## REFERENCES

1. Patel SC, Spaeth GL: Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg* 1995;26:233-36.
2. Brown MM, Brown GC, Spaeth GL: Improper topical self-administration of ocular medication among patients with glaucoma. *Can J Ophthalmol* 1984;19:2-5.
3. Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP: Improving the therapeutic index of topically applied ocular drugs. *Arch Ophthalmol* 1984;102:551-53.
4. Ritch R, Jamal KM, Gürses-Özden R, Liebmann JM: An improved technique of eye drop self-administration for patients with limited vision. *Am J Ophthalmol* 2003;135:530-33.
5. Chrai SS, Makoid MC, Eriksen SP, Robinson JR: Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. *J Pharm Sci* 1974;63:333-38.

Daniel E. Grigera, MD, is assistant professor of ophthalmology, Universidad del Salvador, and head of the glaucoma service, Hospital Oftalmológico Santa Lucía, Buenos Aires, Argentina.

## COMING IN ISSUE 3:

### DIAGNOSIS

- FEATURE: Glaucoma: Diagnosis, Progression and Structure Function Relationships
- UPDATE: Principles Behind New Diagnostic Technologies
- CLINICAL FOCUS: How to Read Printouts
- IN PRACTICE: Disc Assessment

## FUTURE ISSUES

- ISSUE 4: Pseudoexfoliation
- ISSUE 5: Angle closure
- ISSUE 6: Non-IOP Mechanisms
- ISSUE 7: Glaucoma Surgery

14. Diggory P, Heyworth P, Chau G, et al: Improved lung function test on changing from topical timolol: Non-selective beta blockade impairs lung function tests in elderly patients. *Eye* 1993;7(pt 5):661-3.
15. Diggory P: Changing from timolol to betaxolol improves lung function. 1994.(Personal Communication)
16. Lama P: Systemic adverse effects of beta-adrenergic blockers: an evidence-based assessment. *Am J Ophthalmol* 2002;134:749-60.
17. Kirwan JF, Nightingale JA, Bunce C, Wormald R: Beta blockers for glaucoma and excess risk of airways obstruction: population based cohort study. *Brit Med J* 2002;325:1396-7.
18. Diggory P, Heyworth P, Chau G, et al: Unsuspected bronchospasm in association with topical timolol—a common problem in elderly people: can we easily identify those affected and do cardioselective agents lead to improvement? *Age Ageing* 1994;23:17-21.
19. Gandolfi SA, Chetta A, Cimino L, et al: Bronchial reactivity in healthy individuals undergoing long-term topical treatment with beta-blockers. *Arch Ophthalmol* 2005;123:35-8.
20. Kass MA, Heuer DK, Higginbotham EJ, et al. 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* 2002;120:701-13.
21. Singh K, Spaeth G, Zimmerman T, Minckler D. Target pressure—glaucomatologists' holy grail. *Ophthalmology* 2000;107:629-30.
22. Jampel HD: Target pressure in glaucoma therapy. *J Glaucoma* 1997;6:133-8.
23. Zeyen T: Target pressures in glaucoma. *Bull Soc Belge Ophthalmol* 1999;274:61-5.
24. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130:429-40.
25. Membrey WL, Poinosawmy DP, Bunce C, Hitchings RA: Glaucoma surgery with or without adjunctive antiproliferatives in normal tension glaucoma: 1 intraocular pressure control and complications. *Br J Ophthalmol* 2000;84:586-90.
26. Membrey WL, Bunce C, Poinosawmy DP, et al: Glaucoma surgery with or without adjunctive antiproliferatives in normal tension glaucoma: 2 Visual field progression. *Br J Ophthalmol* 2001;85:696-701.
27. Liu JH, Zhang X, Kripke DF, Weinreb RN: Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci* 2003;44:1586-90.
28. Fogagnolo P, Rossetti L, Mazzolani F, Orzalesi N: Circadian variations in central corneal thickness and intraocular pressure in patients with glaucoma. *Br J Ophthalmol* 2006;90:24-8.
29. Drance SM, Crichton A, Mills RP: Comparison of the effects of latanoprost 0.005% and timolol 0.5% on the calculated ocular perfusion pressure in patients with normal-tension glaucoma. *Am J Ophthalmol* 1998;125:585-92.
30. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL: Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 1994;117:603-24.
31. Orzalesi N, Rossetti L, Bottoli A, et al: The effect of latanoprost, brimonidine or a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Arch Ophthalmol* 2003;121:453-7.
32. Olthoff CMG, Schouten JSAG, van de Borne BW, Webers CAB: noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension: an evidence-based review. *Ophthalmology*. In press.
33. Kass MA, Meltzer DW, Gordon M. A miniature compliance monitor for eyedrop medication. *Arch Ophthalmol* 1984;102:1550-1554.
34. Kosoko O, Quigley HA, Vitale S, et al: Risk factors for noncompliance with glaucoma follow-up visits in a residents' eye clinic. *Ophthalmology* 1998;105:2105-11.
35. Patel SC, Spaeth GL: Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg* 1995;26:233-6.
36. Schwartz GF: Persistency and tolerability of ocular hypotensive agents: population-based evidence in the management of glaucoma. *Am J Ophthalmol* 2004;137(1 suppl):S1-S2.
37. Shaya FT, Mullins CD, Wong W, Cho J: Discontinuation rates of topical glaucoma medications in a managed care population. *Am J Manag Care* 2002;8(10 suppl):S271-S277.
38. Migdal C, Gregory W, Hitchings R: Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. *Ophthalmology* 1994;101:1651-6.
39. Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001;85:1028-30.
40. Odberg T, Jakobsen JE, Hultgren SJ, Halseide R: The impact of glaucoma on the quality of life of patients in Norway: 1. Results from a self administered questionnaire. *Acta Ophthalmol Scand* 2001;79:116-20.
41. Janz NK, Wren PA, Lichter PR, et al: Quality of life in newly diagnosed glaucoma patients: The Collaborative Initial Glaucoma Treatment Study. *Ophthalmology* 2001;108:887-897.
42. Nordmann JP, Auzanneau N, Ricard S, Berdeaux G: Vision related quality of life and topical glaucoma treatment side effects. *Health Qual Life Outcomes* 2003;1:75.
43. van der Valk R, Webers CA, Schouten JS, et al: Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology* 2005;112:1177-85.