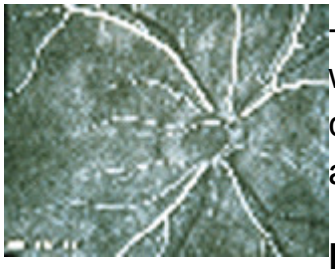
Two new options will make glaucoma therapy safer

Primary Care Optometry News, July 1996

---**Alan Robin, MD**

Alan Robin, MD, an associate professor at Johns Hopkins University, Baltimore, is probably best known for his work with apraclonidine (Iopidine, Alcon) and laser therapy for glaucoma. Here the glaucoma specialist and Primary Care Optometry News Editorial Board member discusses with Staff Writer Susan Biro the coming revolution in medical therapy of glaucoma. Shortly after this interview, the Food and Drug Administration approved Pharmacia & Upjohn's Xalatan (latanoprost) for treating open-angle glaucoma and ocular hypertension in patients who are either intolerant of other intraocular pressure-lowering medications or insufficiently responsive to another pressure-lowering medication.



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Primary Care Optometry News: Before we talk about the new glaucoma drugs moving into clinical use, can you tell us what you think the last major change in glaucoma therapy was?

Alan Robin, MD: The medical therapy of glaucoma was drastically changed in 1978 with the advent of nonselective beta-blockers. Prior to that, glaucoma therapies caused terrible systemic or local side effects. Pilocarpine caused significant browache, miosis and blurred vision, carbonic anhydrase inhibitors had about a 50% acceptability and the original epinephrine drugs had a high rate of allergy.

When timolol came on the market, it was almost as though we had a panacea. It wasn't until approximately 4 years later that we recognized the clinical problems, including depression, bradycardia and decreased pulmonary function. Non-selective beta-blockers alter blood lipids and may increase the long-term risk of stroke and heart disease. Now in all fairness, timolol is very safe in most of those who use it. But its systemic profile and the fact that it is a twice-a-day drug in most individuals are limitations.

PCON: So that brings us to the newest era of post beta-blocker drugs. What are they and what has been your experience with them?

Robin: The most exciting new drug is latanoprost, brand name Xalatan, marketed by Pharmacia & Upjohn. I was one of the investigators in the U.S. studies.

Xalatan is a much more powerful drug than timolol. Timolol given twice a day has a mean eye pressure lowering effect of 25%. Latanoprost given once a day has a mean intraocular pressure (IOP) lowering of about 35%, so it's a third more powerful. It also adds well to most of the other medications that we have.

PCON: Why is that?

Robin: It works by a different mechanism of action than any of the other classes of drugs we have. Beta-blockers, alpha agonists and carbonic anhydrase inhibitors basically "turn the faucet down," or decrease the production of aqueous humor. Pilocarpine "opens the drain" by letting more fluid exit through the trabecular meshwork. Latanoprost works by increasing the outflow of fluid through a new pathway: uveoscleral outflow.

This is an escape path where fluid basically goes behind the iris through the suprachoroidal space. Latanoprost allows this outflow by relaxing ciliary muscle fibers in a dose-dependent way and also by increasing the intracellular spaces within the trabecular meshwork. It is not dependent on episcleral venous pressure. It may be ideal in low-tension glaucoma patients.

I was also involved with a compassionate-use study that enrolled patients on maximal medical therapy who were surgical candidates but didn't want surgery. Prostaglandins worked beautifully on that kind of patient. Latanoprost also has no effect on blood flow, on blood-aqueous barrier or the retinal vasculature.

It's also an ideal prodrug in that there is no backward flow within the tear cell. This minimizes systemic side effects that might occur through systemic absorption.

PCON: Does it have any adverse effects?

Robin: There are three potential complications with this drug. One is hyperemia. In earlier models of prostaglandins hyperemia was a real problem. Patients' eye-pressure lowering was great, but they had terribly red eyes. With latanoprost, the redness is about 0.5 on a scale of 0 to 5. The injection peaks at about a half hour after it's given and is gone within an hour and a half. And because it's given once a day—at nighttime, because it seems be more efficacious then—the patient is sleeping during most of the time the eye is red.

Another potential complication in about 3% of patients—those with bluish brown, greenish brown or hazel eyes— is that the eye can turn more brown.

PCON: Is this part of an ongoing change in the eye?

Robin: No, this is not a premalignant condition. It's just an eye color change of the type that has been seen with prostaglandin use in dermatology. It's something that patients should be aware of. However, most patients accept it because they realize the gravity of their disease and because they can get a once-a-day eye drop.

The third potential problem with prostaglandins is that they can cause inflammation. We looked carefully for signs of inflammation but have not been able to find any significant inflammation associated with latanoprost, which is really exciting. I think it's the most exciting new drug to enter the field of glaucoma therapy in the last 20 years.

PCON: Where will it fit into your plan for primary open-angle glaucoma treatment?

Robin: My feeling is that unless somebody is young and has blue-green eyes, today, with the knowledge I have, I would rather be on latanoprost than a beta-blocker. One of the problems with the nonselective beta blockers is that they all decrease exercise-induced tachycardia. The blunting of exercise-induced tachycardia makes it harder for the body to cope with normal daily activities and stress.

In most patients, latanoprost will become my first drug of choice. If it is not adequate, I would probably add a cardioselective beta-blocker, such as betaxolol.

PCON: You said latanoprost adds well to most other current glaucoma medications. Are there any drugs to which it is not additive?

Robin: There are some human data from Scandinavia indicating that it adds to pilocarpine, but other data with 4% pilocarpine showed that it does not add any effect. It is still being studied.

PCON: The other new drug, still in clinical trials, is Allergan's brimonidine tartrate.

Robin: Brimonidine is actually an old drug. It's an alpha agonist that has been available for many years, but no ophthalmic work was done until about the last 10 years.

Clonidine was sort of the classic alpha-2 agonist. It was originally looked at as a nasal decongestant, but in early studies volunteers were fainting because their blood pressures dropped suddenly. So it was used as a blood-pressure lowering medicine. Then it was noticed that systemic clonidine also lowered eye pressure. Since that worked, someone decided to try it as eye drops.

In 1981, Elizabeth A. Hodapp, MD, compared topical clonidine to pilocarpine 2% and it worked very well, except for the large drops in blood pressure. Clonidine is no longer used as a therapy in the United States, but it's still currently available in Germany.

Next came apraclonidine, brand name Iopidine, marketed by Alcon. I did much of the clinical work on apraclonidine, a relatively selective alpha-2 agonist. It is probably the safest drug we have seen so far in the therapy of glaucoma. The only disadvantage to apraclonidine is that 15%-25% of patients develop a localized allergy involving the eyes, the eyelids and surrounding skin. It is a self limiting allergy, but it's disconcerting.

With regard to the more serious side effect of the class of alpha agonists—systemic hypotension—the concept of therapeutic index comes into play.

Therapeutic index is a measure of the difference between the safety of a certain drug's concentration and its efficacy. Apraclonidine has a large difference between its effective dose and the level that causes side effects. So it's a very safe drug.

PCON: Did you participate in the studies of brimonidine as well?

Robin: I was involved with both the design and clinical evaluations of some of the original dose-response studies for brimonidine, both safety studies and post-laser use studies. I have not been involved with the chronic-care studies, but I am familiar with some of their results. I've also been involved with a compassionate-use study with brimonidine.

My clinical experience has been limited, but in this limited experience I have had a few patients who became drowsy. Some of these patients have been rechallenged with the drops, and without the drops they feel fine. Start them on the drops again, and they're falling asleep. But the 1-year studies of brimonidine do not seem to have this as a major finding.

The allergy problem is much less than is seen with apraclonidine. But the blood pressure effects and central nervous system effects both potentially concern me.

PCON: What kind of therapeutic index does brimonidine have?

Robin: Fairly tight. In the initial studies for the post-laser indications, a 0.5% concentration was used. With 0.5%, there was a statistically significant drop in blood pressure even with one drop. The 0.2% solution appears to be much safer, so that is what is in clinical trials now.