Optometrists’ prescribing privileges are changing in Canada and the U.S., and it is therefore of paramount importance that everyone keeps abreast of emerging pharmacological products. It is also important to clarify what we have collectively learned about time-honored products, some of which have been used for decades.

This supplement is a comprehensive overview of products that are currently available in our anti-glaucoma armamentarium. It covers most classes of glaucoma agents, with an emphasis on the most effective topical medications for lowering intraocular pressure (IOP), as well as newer ocular hypotensive agents.

Glaucoma is a complicated disease process that is significantly under-diagnosed. Our understanding of the disease process and its mechanisms has been in a constant state of flux for the last three decades. We have evolved from having only pilocarpine (and other miotics) and timolol, to having a complete arsenal comprised of multiple drugs from five classes. A significant number of glaucoma patients — the majority, in fact — can now be managed medically and may never require an operation. Still, surgery remains a viable option for those patients who need it.

The last 20 years have also brought about significant improvements in surgical techniques, advancements in technology, and newer, safer lasers. Still, many areas remain to be explored, and the concept of neuro-protection remains a hot topic of debate and controversy. If the last few decades have taught us anything, it is that change is inevitable and what is novel today will soon become old news. Expect the glaucoma field to look vastly different ten years from now.

Whatever our direction, optometry will surely be on the front lines of eye care. If there is a way for optometry to profoundly impact public health care, I surmise that it will be in the area of chronic glaucoma care. Optometrists are ideally trained and suited to care for patients with this chronic disease, due to its slow and progressive nature. Each and every one of us needs to recognize that glaucoma care should be a part of our every day practice.

It is my sincere hope that you will find this supplement helpful in your own practice as you treat glaucoma patients.

With Warmest Regards,

Gregory M. Schultz, OD, FAAO
Case

A 74-year-old African-American female was referred for floaters OS, of four days duration. She described no significant decrease in vision, but noted a few small spots in her vision that “would come and go.” Her medical history was negative for diabetes and CVA, but she did have hypertension. Her medications included loratadine, clonidine HCL, and Benicar. Ocular history was negative for prior glaucoma, trauma/injury, blood loss, hypotensive episodes, transfusions, Reynaud's phenomenon, and migraines. There was no prior history of eye surgery.

Distance visual acuity was OD 20/20-2, OS 20/20 with normal color vision. Pupil testing was normal; no APD was noted. The external exam was normal.

The slit lamp examination showed clear corneas with arcus OU; anterior chambers were deep and quiet and there were lens changes of 1+ cortical spoking and 2+ nuclear sclerosis OU. Initial IOP was measured at OD 20, OS 20 at 3:22 p.m. The dilated fundus exam revealed an interesting finding: the vitreous showed syneresis without PVD or pigment OU, and the macula was clear OU. The optic nerve was flat, pink, and healthy OD, but there was a large hemorrhage superiorly off the nerve OS. The cup to disc ratio was .60/.70 OD and .55/.60 OS. The retinal vessels were attenuated. No other retinal hemorrhages or cotton wool patches were seen in the posterior pole or periphery OU.

The patient was diagnosed with hypertensive retinopathy, mild and new optic nerve hemorrhage OS, suspected hypertensive hemorrhage versus drance heme, and COAG suspect.

Due to the acute symptoms and her age, a blood work-up was ordered including an ESR, CRP, CBC with differential, fasting blood glucose, and HgA1C. The patient was asked to follow-up with her primary care physician for a recheck of her blood pressure and the heme was documented with a digital photo (see Figure 1). A Carotid Duplex Study was also ordered to rule out carotid occlusive disease or an embolic event. We planned to see the patient back for further testing at a follow-up visit; pachymetry, gonioscopy, visual fields, and nerve fiber analysis were ordered.

On the first follow-up appointment, the PACH was OD 518, OS 521 microns. IOP measured 20 OD, 18 OS at 8:20 a.m. Gonioscopy was open grade 3-4 360° OU with mild plateau iris configuration OU. The VF showed a questionable superior nasal step in the right eye (see Figure 2). GDX nerve fiber analysis showed a normal nerve fiber layer in both eyes (see Figure 3). All of her blood work was normal and there were still no symptoms consistent with Giant Cell Arteritis.
A second follow-up visit (5 months later) revealed a pressure of 16 OD, 15 OS. A subsequent dilation was performed. Optic nerve head presentation at the second follow-up visit showed new optic nerve hemorrhage in the OS, this time inferiorly. There was an inferior wedge nerve fiber layer defect clinically visible in both eyes (see Figure 4). Repeat VF testing showed a better defined superior nasal step OD and a superior paracentral scotoma OS (see Figure 5). A Carotid Duplex Study was ordered to rule out recurrent embolic events secondary to medical history and variable clinical presentation. The Doppler showed no hemodynamically significant stenosis or plaquing. We initially planned to consider treatment for glaucoma due to the clinical presentation and VF defect despite the low IOP on follow-up. The patient was placed on Travatan Z and asked to return in 1 month. On her return visit, the IOPs measured OD 13, OS 14 at 8:44 a.m.

This case illustrates how a diagnosis of glaucoma can be complicated and illusive when pressures are not significantly elevated and new imaging technologies give us erroneous information that is inconsistent with our clinical impressions. This case also points to how we should never become dependent on imaging technologies, no matter how advanced, to make the diagnosis. Rather, we must combine the information and data that technology provides, with our own clinical findings and impressions to create a composite picture of each patient’s condition.

**The Miotics**

This review emphasizes the newest drugs in glaucoma management, and therefore, it will not focus on time-tested treatments that are being overtaken by more effective alternatives - those that are better tolerated and have fewer side effects. That said, any glaucoma pharmacology review must have a place for miotics, as they play a key role that no other class or agent can fill.

Acute narrow angle glaucoma and angle closure glaucoma - whether acute or chronic - are two of the most damaging glaucomas we face, as they can both involve extreme pressure spikes and rapid deterioration of optic nerve status. Although most classes of glaucoma agents can be employed to treat elevated pressure in an angle closure attack, nothing can physically break the attack like miotics.

The gold standard in miotic therapy is pilocarpine, a non-selective muscarinic receptor agonist. It is available in 0.5%, 1%, 2%, 3%, 4%, and 6% solutions. In acute angle closure glaucoma management, 1-2% solutions are usually sufficient to con-
strict the pupil and remove or pull the iris tissue from the angle. This treatment is typically used until a laser PI can be performed. Long-term pilocarpine therapy is rarely necessary or tolerable after PI. Side effects from pilocarpine can include blurred vision, brow headaches, and a dimming of vision secondary to pupillary miosis. It is thus a poor choice for chronic care, except in cases of asymptomatic elderly patients who have been on this medicine for years to treat chronic narrow angle glaucoma. Typically, miotics are best avoided in pre-presbyopic patients. Angle closure is not always obvious, especially when it is chronic, as adaptation, time, and other compensatory mechanisms can eliminate some of the hallmark corneal edema. An astute clinician will make this diagnosis via gonioscopy.

**Beta-Blockers**

This class of medications is one of the most widely used and efficacious groups of medicines for glaucoma. Beta-blockers came into use for glaucoma management in the late 1970s. This category provides us with some of the best drugs in our anti-glaucoma arsenal, as they commonly decrease IOP by 25%, by reducing aqueous humor production. They have withstood the test of time, and our experience with these agents has taught us several key lessons that are still pertinent.

The mechanism of these drugs is the beta-adrenergic blockade of non-pigmented ciliary body epithelium cells. The result is the suppression of aqueous production. Most beta-blockers are termed non-selective, meaning they block
both beta-1 and beta-2 receptors on the ciliary body epithelium. Timolol, levobunolol, and metipranolol fall into this category. There is also one beta-1 selective (cardio-selective) agent (betaxolol) that was specifically developed for “reduced” pulmonary side effects. However, experience with this agent has shown that even selective beta-blockers do exhibit some cross over reactivity to beta-2 receptors.¹ Thus, newer agents outside this class would likely be safer for patients with high risk pulmonary histories.

The side effects of this class have long been considered its Achilles heel. These drugs can induce bradycardia and can cause a general decrease in the heart rate and the force of the heart’s contractions. Bronchiolar constriction in the lungs is another side effect due to the beta-2 receptor blockade on the bronchial smooth muscle.¹ Therefore, these drugs are contra-indicated in any patient with bradycardia, asthma, and COPD.

Most beta-blockers come in 0.25% and 0.50% formulations. Experience and the literature have taught us that the 0.25% concentration is just as effective as 0.50%. The 0.25% formulation is at the top of the dose response curve, which means that higher concentrations of the drug are unnecessary, as the maximum therapeutic effect can be attained with a 0.25% dosage with fewer systemic side effects.² There is one important caveat, to this: since melanin pigment absorbs some of the drug, 0.5% is used by some clinicians to treat patients with darkly pigmented skin and irides. It is important to note that several studies have compared QD to BID dosing of beta-blockers, and little to no difference has been shown in the IOP-lowering effect with more frequent dosing. Timolol and levobunolol are both non-selective beta-blockers that are available in 0.25% and 0.50% formulations. They are the only beta-blockers that have sufficiently extended half-lives, making them just as effective for QD dosing. Also note that because aqueous production naturally slows during sleep, when the adrenergic system is at rest, beta-blockers are best used shortly after waking in the morning.²

The only cardio-selective beta-blocker is betaxolol. It comes as a 0.25% suspension and has slightly less of an effect on IOP than non-selective beta-blockers. There is definitely a lower risk for pulmonary compromise with the use of betaxolol. Crossover reactivity to beta-2 receptors has been observed with betaxolol, as previously mentioned, and this point is worthy of emphasis. In previous years, Betoptic-S was also touted as having potential neuroprotective properties. This claim was supported by a study that seemed to show that glaucoma patients on betaxolol had enhanced preservation of their VFs compared to those taking other agents. Short of this one study, there seems to be little evidence to substantiate the claim.

Metipranolol (Optipranolol, Bausch & Lomb) is another non-selective beta-blocker. It is inexpensive and effective, and is available in a 0.3% solution. Its indication is for BID dosing, and no studies have been done on QD dosing. Its efficacy is comparable to that of other non-selective beta-blockers.

Levobunolol hydrochloride (Betagan, Allergan) is also a non-selective beta-blocker with efficacy and side effects that are similar to other non-selective beta-blockers. Still, it has one important distinction: it has the longest half-life of all the drugs in its class, and it is thus the best suited to QD dosing.

Gel-forming solutions, such as Timoptic XE and its generic equivalents were developed in an attempt to simplify beta-blocker therapy and increase compliance. The gels were a novel idea, but because the half-lives of some beta-blocker solutions were found to be long enough for effective QD dosing, the novelty was essentially negated. Gel-forming solutions tend to be slightly more expensive than normal solutions and do not have significantly better duration of action than typical solutions with demonstrated extended half-lives (timolol, levobunolol). Note that there are only two brand name protected beta-blockers: Betimol (timolol hemihydrate) and Istalol (timolol maleate). Betimol has the advantage of being available in both a 0.25% and a 0.5% solution.

Many practitioners who routinely treat glaucoma recognize that we frequently see patients with extreme sensitivities and reactive hyperemia due to single or multiple medications used topically. There are several good pharma-
Pharmaceutical choices for these patients. Timoptic (timolol maleate 0.25% or 0.50%) is available in an Ocudose (preservative-free) format, however, this formulation is not available in Canada. This medication is especially useful for patients who are sensitive to benzalkonium chloride (BAK) or for patients using multiple drugs, each with its own preservatives. It is worth mentioning that most of the glaucoma agents are preserved with BAK, with the exception of several products: Timoptic Ocudose (unavailable in Canada), Travatan-Z (Sofzia), Alphagan-P (Purite 0.005%). It should also be noted that in Canada there are two other preservative-free offerings not available in the United States: Cosopt and Trusopt are available as preservative-free formulations, available in unit dose pipettes. These agents have no preservatives at all, much like Timolol Ocudose, and therefore present viable options for patients with hypersensitivities to preservatives of any type. All are prudent choices for patients with hypersensitivity or toxicity issues due to multiple medications or preservatives.

Carteolol (Ocupress, Novartis and generics) is a non-selective beta-blocker that has been shown to possess “intrinsic sympathomimetic activity.” This phenomenon describes a drug that can show both agonism and antagonism at a given beta receptor. This drug has the advantage of relatively safe use in patients with borderline heart rates; a borderline heart rate is otherwise a relative contraindication to the use of other non-selective beta-blocking agents. Carteolol is believed to mildly stimulate the heart rate, avoiding bradycardia in patients with borderline heart rate. This allows a subset of patients to enjoy the benefits of using a beta-blocker, when they might not otherwise have the opportunity to use these agents. This was a larger issue prior to the widespread use of prostaglandin analogs.

Practitioners need to pay close attention to patients’ systemic medications when prescribing beta-blockers, as many hypertensive patients may be on oral beta-blockers and other cardiac medications. Changes in systemic therapy can have a profound effect on the stability of the IOP (and possibly on cardiac status) when patients are simultaneously taking topical beta-blockers.

The effects of topical beta-blockers in these patients can be additive and can slow the heart rate, thereby creating bradycardia, cardiac arrest, or serious pulmonary symptoms or complications. Finally, the effects of topical beta-blockers on IOP are blunted by the concomitant use of oral beta-blockers. Look to other adjunctive agents outside this class if your patients are already taking oral beta-blockers.

**Prostaglandin Analogs**

This class was developed to establish a new gold standard in glaucoma therapy, beyond beta-blockers. The goals were to maximize the IOP-lowering effect, simplify dosing, and minimize the side effect profile. Those goals were achieved with the advent of prostaglandin analogs. This drug class has existed for over a decade and has earned its place as the new first-line agent of choice.

**Mechanism of Action**

The drugs in this class are prodrugs that require hydrolysis by corneal enzymes before they become active free acids. The free acids bind to FP receptors in the ciliary body. Activation of these receptors upregulates matrix metalloproteinases (MMPs), which degrade extracellular proteins (i.e., collagen) in the uveoscleral pathway. The result is an increase in uveoscleral outflow and a lowering of the IOP. These drugs also enhance outflow, to some degree, through the trabecular meshwork. Thus, they facilitate the egress of aqueous completely through every conceivable avenue – this is why they are such potent ocular hypotensive agents.

Prostaglandin analogs have become the drugs of choice, when not contraindicated. As they are structurally similar to prostaglandins, these drugs have the potential to incite inflammation in the anterior and posterior chamber.
Therefore, they are contraindicated in patients with a history of recurrent uveitis and CME, and would need careful consideration for use in patients with epiretinal membranes. Some surgeons have advocated discontinuing these medications in the acute post-operative period for cataract patients. Although this makes perfect sense, the incidence of CME is so low that many have abandoned this practice and allow patients to continue with this therapy, largely as a matter of practicality. There are three drugs in this class: latanoprost (Xalatan, Pfizer), travoprost (Travatan, Travatan-Z, Alcon), and bimatoprost (Lumigan, Allergan). Studies show that all three are nearly equal in their IOP-lowering effects, but not in their side effect profiles. Latanoprost was the first of the three to be approved and it has changed the way we manage glaucoma medically.

All drugs in this class share similar side effects, however, some have more profound effects than others. The most common side effect of this class – and the most irritating for patients – is conjunctival hyperemia. This is by far the most common reason for patient dropout within this class. Hyperemia tends to be least significant with the use of Xalatan and most significant with the use of Lumigan (0.03% Bimatoprost). Travatan falls somewhere in the middle in this regard. Allergan recently released a new lower concentration of Bimatoprost 0.01% (Lumigan RC) which has shown no significant difference in IOP-lowering ability when compared to the 0.03% formulation, but it does have a significantly enhanced tolerability profile. This newer lower concentration formula has shown significantly improved tolerability over a 12-month trial when compared to the 0.03% formulation. Furthermore, there was a 23.5% relative reduction in the incidence of treatment related conjunctival hyperemia adverse events with the lower concentration, which is clinically relevant. A 12-month randomized clinical study by Katz et al. also found that treatment-induced hyperemia with the 0.01% formulation was less common and less severe, ultimately leading to statistically significantly fewer discontinuations from treatment.

Other side effects of this drug class include hypertrichosis of the eyelashes, and hyperpigmentation of the periocular skin. The latter is a reversible phenomenon once the drug is stopped. This side effect tends to be more prominent in fair skinned individuals than in darkly pigmented people. The cosmesis is an issue for both men and women and should be considered when treating unilateral glaucoma. The hypertrichosis is arguably a favorable side effect for some. It actually led to the development and launch of a topical application of the same medicine called Latisse (Allergan), specifically for the purpose of enhancing eyelash appearance.

Finally, a darkening of the iris tissue – particularly in patients with mixed color irides (hazel, green, green to light brown) – is a well-documented side effect within this class. This phenomenon is unlikely in people with blue or brown eyes. Latanoprost, as described, has the lowest incidence of hyperemia. It also has a low incidence of CME associated with its use.

The prostaglandin analogs are attractive agents for optometrists and ophthalmologists because of their simple dosing regimens and their maximum IOP-lowering effects. These drugs stand alone in their efficacy as single agents and can achieve up to a 30% reduction in IOP on QD dosing. They are all dosed QD, and were originally thought to have the best effect when dosed at night. However, time and experience have shown there to be little difference in hypotensive effect, whether they are taken in the morning or in the evening.

Another frequent observation within this class is an extended duration of action. In my experience, the reduced IOP seems to last several days, even after non-compliance. These drugs may thus be a good choice for patients who forget doses from time to time. In a study by S. Kurtz and G. Shemesh, it was demonstrated that once-weekly dosing with latanoprost was as effective at lowering IOP as once-daily dosing. This same long lasting hypotensive effect has been demonstrated with Travatan. This phenomenon confers significant advantages to the drugs in this class. This is a significant discovery given the statistics on non-compliance within the glaucoma patient population.
Travatan comes in two formulations: Travatan and Travatan Z. The only difference is the preservative used in each formula; Travatan Z uses boric acid propylene glycol, sorbitol and zinc chloride (Sofzia®) instead of BAK. Proprietary research on Travatan has shown that on average, its hypotensive efficacy is slightly better in the African-American population than in the Caucasian population. The company has previously used this fact in its marketing campaigns.

Lumigan was the last drug released in this class and it has powerful ocular hypotensive effects. In some cases, we have seen 50% reductions in IOP when used as a single agent. Unfortunately, a fair number of patients on this medication develop chronic and intolerable hyperemia. Still, the initial hyperemic effects experienced by some patients tend to dissipate with time. If the hyperemia is tolerable at two or three weeks, it will likely improve with time on this medication. Beyond several months, the hyperemia is not likely to improve. The advent of Lumigan RC will likely remedy much of the issue with hyperemia.

These drugs all pair nicely with once daily beta-blocker therapy for a simple but potent combination with excellent IOP reduction on a BID-dosing regimen. This is ideal for most patients, for as we all know, decreasing the complexity of a medical regimen results in improved compliance. There is nearly equal efficacy among all drugs in this class, and one can expect 30% or greater reductions in IOP on QD dosing with no appreciable systemic side effects. It is hard to imagine a better first line agent than the prostaglandin analogs.

Topical Carbonic Anhydrase Inhibitors (CAIs)

There are two drugs in this class – Trusopt and Azopt – and both work well as adjunctive therapy to the drugs previously mentioned. When initially studied, both drugs received labeling for TID dosing, but most practitioners use BID dosing with near equal results in terms of IOP reduction. If used as stand alone agents, these drugs will achieve better control with TID dosing. Both drugs will achieve about a 15% reduction in IOP.

Trusopt (Dorzolomide 2%, Merck) is a solution that, comparatively speaking, has a low pH of approximately 5.6. This causes a fair amount of stinging on instillation, which is the drug’s only downside. The stinging can be significant enough to cause some patients to discontinue treatment. Those who find the medicine tolerable receive the benefit of a potent ocular hypotensive that works by aqueous suppression. Practitioners should bear in mind that topical CAIs do not lower IOP as significantly as oral CAIs, however, there are obviously fewer side effects. Note that Trusopt Preservative-Free is available in Canada in unit dose pipettes. A generic version of Trusopt is now available in the U.S. (not in Canada) for a substantially decreased price.

Azopt (Brinzolamide, Alcon) is its counterpart, and is available as a 1% suspension. Alcon’s unique suspension requires very little bottle shaking in order to evenly disperse the drug in the suspension. This proprietary suspension is also used in Betopic-S and Vexol. Azopt has a higher pH (7.5), which accounts for its enhanced ocular tolerability.

These drugs make adequate adjunctive agents but are not generally used as first line therapy. Although these are sulfa-based drugs, recent studies and reviews suggest there is probably little cause for allergy concerns with these drugs, even in patients with a history of allergic reaction to sulfa-based antibiotics.
It is worth mentioning that topical CAIs do not decrease IOP as much as oral CAIs (approximately 15-20% versus 30%). In patients taking oral CAIs, the effects of a topical CAI may be blunted.

**Alpha Agonists**

There is only one clinically relevant drug in this class for chronic use: brimonidine (Alphagan or Alphagan-P, Allergan). The other option is apraclonidine (Iopidine), which has such a high propensity for ocular toxicity, hyperemia, and hypersensitivity, that it has been relegated to use in post-op laser treatment patients. The alpha agonists stimulate alpha receptors in the ciliary body, iris, and trabecular meshwork, and primarily inhibit aqueous production. However, they also have been shown to a lesser degree to stimulate uveoscleral outflow, thus creating a combined mechanism for potent IOP reduction.

Brimonidine is available in three concentrations: 0.2% (Alphagan), or 0.15% and 0.1% (Alphagan-P). These concentrations show little difference in their efficacy data and can reduce IOP by 20-25%. These drugs slowly begin to lose their effectiveness 8 hours after instillation, hence, they were dosed TID in the FDA labeling studies. If these drugs are used as mono-therapy, they are best dosed TID for around-the-clock IOP control. When used as adjunctive therapy, most clinicians choose to dose BID, typically in conjunction with a beta-blocker or a prostaglandin.

**Combination Medications for Glaucoma: The New Frontier**

**Background**

The current wave of glaucoma treatments focuses on new delivery systems for established drugs. Our anti-glaucoma arsenal is stocked, and there are several reasons that fixed combination drugs make sense, however, there are advantages and disadvantages to these drugs, which we will review in full detail. Note that in order for fixed combination drugs to work properly, the two drugs must be compatible in several ways. Each component must be soluble at a similar pH and both components must have similar dosing regimens. The main reason for the development of fixed combination products was to simplify therapy, and thus increase patient compliance. In addition to making the treatments simpler, patient costs might be cut if fewer bottles of medicine were required for treatment.

Patients often take more than one topical medical therapy to reach a target goal. In fact, the Ocular Hypertension Treatment Trial showed that 40% of patients needed more than one medication to achieve a 20% reduction in IOP.
Timing the application of several medicines in order to achieve maximum therapeutic effect can needlessly complicate treatment. When multiple medications are necessary, patients spend more time applying the medications. In our fast-paced society, waiting 15–20 minutes to apply eye drops may not be realistic. Patients who are anxious to get on with their day often rush their applications, and may create a washout effect if medications are administered too closely together. This effect can be avoided with fixed combination drugs. Finally, there should be less cumulative preservative exposure and toxicity in combined products, as fewer cumulative preservatives are applied to the ocular surface.

Disadvantages of Fixed Combinations
There are several difficulties to consider before prescribing fixed combinations. First, there is no dosing flexibility. Note that if a patient would do well with QD beta-blocker therapy, this is not an option with a fixed combination drug that is prescribed BID, such as Cosopt or Combigan. This can lead to overtreatment with beta-blockers. Second, the concentrations are fixed and will thus lead to excessive treatment in some patients who only require lower concentrations of the individual drugs.

Combination Drugs
Several of the combination drugs already in use have established themselves as good adjunctive therapies; they are largely second line agents. Currently, all of the combination products combine an adjunctive agent with timolol, a non-selective beta-blocker.

Cosopt has been used in Canada and the U.S. since 1998 and it provides approximately a 15% reduction in IOP over and above a non-selective beta-blocker used alone. It is a combination of 0.5% Timolol Maleate and 2% Dorzolamide HCL and is dosed BID. It is indicated in patients who are taking a beta-blocker, but who have not quite reached their target IOP. This drug is good for approximately a 30% reduction in IOP, which makes it comparable to a prostaglandin analog. In one study, Cosopt and latanoprost were measured at four points in the day, and they equally reduced the IOP from an untreated baseline. Cosopt is now available in a generic formulation in the US, however, it is not available in Canada. The preservative-free version of this combination product should fill an important medical niche for patients suffering from toxicities from preservatives. There is no other combination product available that can currently make that claim.

Combigan is also dosed BID and combines 0.5% timolol maleate and 0.2% brimonidine tartrate, an alpha-adrenergic agonist. It is also an excellent choice for patients who are taking a beta-blocker, and who cannot seem to achieve target levels. The drug is comparable in its efficacy to Cosopt and can decrease IOP by as much as 30%. One would think that the concentration of brimonidine and its preservative in this combo agent would logically make it more allergenic than the 0.1%, or 0.15% formulation of Alphagan-P. However, in actuality, the combined formulation of Combigan has shown to have a significantly lower incidence of ocular allergy than Alphagan 0.2% and a slightly lower incidence of allergy than even Alphagan-P. It is believed that the timolol in the combination product blunts the effect of enhanced tissue penetration seen with adrenergic agonists, which may be responsible for the decreased incidence of ocular allergy.

The side effects and contraindications for the combination medications are the same as for their individual components. It is important to note that dosing with a fixed combination drug may not be optimal for some patients. In some cases, the individual agents allow for greater customization of dosing regimens as well as drug concentrations.
The newest combination drugs include Xalacom (latanoprost/0.5% timolol), Duotrat (travoprost 0.004%, 0.5% timolol) and Azarga, (bimatoprost/timolol). These drugs all combine prostaglandin analogs with timolol, which for years has been the gold standard in glaucoma therapy.

Xalacom (Pfizer) combines two potent ocular hypotensive agents into one bottle, thereby providing a powerful combination for lowering IOP. Its QD dosing makes the medication even more attractive, as compliance is likely improved and side effects minimized. It was released in 2001 and is available worldwide except in the U.S. When compared in a study with Cosopt BID, it produced a 1mm better reduction in IOP. Xalacom dosed in the evening provided better IOP reduction for a 12-hour daytime diurnal curve compared to Alphagan 0.2% and Timoptic 0.5%, both dosed separately BID.

Duotrat (travoprost 0.004%, timolol 0.5%, Alcon) is currently approved in Australia, Europe, and Canada, but not in the U.S. Duotrat is already approved in Europe and Canada for QD dosing. Efficacy should be comparable to Xalacom.

Azarga (Alcon) was fairly recently approved in Canada for the treatment of elevated IOP associated with open-angle glaucoma or ocular hypertension in adult patients for whom monotherapy provides insufficient IOP reduction. Alcon’s proprietary research has shown the drug to be better tolerated than Cosopt in their head to head patient preference studies. Since both drugs are dosed BID, some believe compliance may be better with Azarga BID due to its potentially enhanced tolerability.

These drugs all have 0.5% timolol in common and, as previously stated, all of the prostaglandin analogs are nearly equal in their ability to lower IOP. Therefore, we expect these three combination agents to be equally efficacious. Some of us may prefer QD dosing to BID dosing and simplicity of dosing may be the deciding factor for some patients if efficacy is proven to be equal for these new agents. Further study and head to head comparisons for efficacy of hypotensive effect need to be conducted between these latest agents before any advantages can be claimed by one over another. They all have the same Achilles heel — a non-selective beta-blocker, which must be taken into consideration as always with our patients with borderline heart rate and pulmonary compromise. Due to the inflexibility inherent in fixed combination products, practitioners may prefer, if efficacy is equal, to lean toward QD products in this class to minimize or avoid the effects of potentially over-treating with a 0.5% beta-blocker.

**Conclusion**

More groundbreaking pharmacological products have been produced for glaucoma in the last 15 years than in almost any other field in eye care. Treatments will undoubtedly progress as research continues on neuro-protection, new agents and combinations, new technologies, and new surgical treatments, including the newer micropulse laser and trabectome surgeries.

As our population ages, the incidence of glaucoma will undoubtedly rise and the number of glaucoma patients in our practices will grow. Optometry must be ready for the large numbers of patients who will present with this medically manageable disease; we must be capable and prepared to care for a growing population of glaucoma patients, as optometrists will play an important role in the management of these patients.

**Corresponding Author**
Gregory M. Schultz, OD, FAAO
gschultz@advancedvision.org
Disclosure

The author has no affiliation with, or financial involvement in, any entity that holds a direct financial interest in the subject matter discussed in this manuscript.

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Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor fleckles of the iris are expected to be affected by treatment.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. See Part III Consumer Information of the Product Monograph.

**Ophthalmologic**

LUMIGAN® RC should be used with caution in patients with active intraocular inflammation (e.g. uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution 0.03%.

LUMIGAN® RC should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN® RC has not been adequately evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

The pivotal clinical studies included patients with pseudophakotic and pigmentary glaucoma, in numbers proportionate to the population. All of these patients responded positively, however given the low absolute numbers of these patients enrolled no statistical significance can be concluded. None of these patients dropped out due to lack of efficacy or adverse experiences.

Contact lenses should be removed prior to instillation of LUMIGAN® RC and may be reinserted 15 minutes following its administration. Patients should be advised that LUMIGAN® RC contains benzalkonium chloride, which may be absorbed by soft contact lenses.

The benzalkonium chloride concentration in LUMIGAN® RC is 0.02% (0.2 mg/mL), compared to 0.005% (0.05 mg/mL) in LUMIGAN®. Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

LUMIGAN® RC has not been studied in patients with severe dry eye, and therefore, should not be used in patients with severe dry eye (see WARNINGS and PRECAUTIONS of Product Monograph).

**Adverse Reaction Seriousness and Incidence**

(see Supplemental Product Information for full listing)

In the 12-month multi-centre, double blind, active controlled clinical study with bimatoprost ophthalmic solution 0.01%, most adverse events were ocular, mild, and not serious. The most frequently reported adverse event was conjunctival hyperemia (31.4% of patients treated).

In the controlled clinical trial, compared to LUMIGAN® RC, significantly fewer adverse events were reported with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving.

In the 12-month multi-centre clinical study with bimatoprost ophthalmic solution 0.03%, one drop/day in both eyes for 14 days.

In a 12-month clinical study, iris colour change was reported in 0.5% of patients treated with bimatoprost ophthalmic solution 0.01%. Noticeable darkening of the iris has been reported in 1.5% of patients treated for 12 months with bimatoprost ophthalmic solution 0.03% at the proposed dose of one drop once daily in each affected eye (1.1% of patients treated for 6 months).

Patients should be informed of the possibility of iris colour change. In addition, patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, peribulbar tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor fleckles of the iris are expected to be affected by treatment.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. See Part III Consumer Information of the Product Monograph.

**Ophthalmologic**

LUMIGAN® RC should be used with caution in patients with active intraocular inflammation (e.g. uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution 0.03%.

LUMIGAN® RC should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN® RC has not been adequately evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

The pivotal clinical studies included patients with pseudophakotic and pigmentary glaucoma, in numbers proportionate to the population. All of these patients responded positively, however given the low absolute numbers of these patients enrolled no statistical significance can be concluded. None of these patients dropped out due to lack of efficacy or adverse experiences.

Contact lenses should be removed prior to instillation of LUMIGAN® RC and may be reinserted 15 minutes following its administration. Patients should be advised that LUMIGAN® RC contains benzalkonium chloride, which may be absorbed by soft contact lenses.

The benzalkonium chloride concentration in LUMIGAN® RC is 0.02% (0.2 mg/mL), compared to 0.005% (0.05 mg/mL) in LUMIGAN®. Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

LUMIGAN® RC has not been studied in patients with severe dry eye, and therefore, should not be used in patients with severe dry eye (see WARNINGS and PRECAUTIONS of Product Monograph).

**Adverse Reaction Seriousness and Incidence**

(see Supplemental Product Information for full listing)

In the 12-month multi-centre, double blind, active controlled clinical study with bimatoprost ophthalmic solution 0.01%, most adverse events were ocular, mild, and not serious. The most frequently reported adverse event was conjunctival hyperemia (31.4% of patients treated).

In the controlled clinical trial, compared to LUMIGAN® RC, significantly fewer adverse events were reported with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving.

In the 12-month clinical study with bimatoprost ophthalmic solution 0.03%, one drop/day in both eyes for 14 days.

In a 12-month clinical study, iris colour change was reported in 0.5% of patients treated with bimatoprost ophthalmic solution 0.01%. Noticeable darkening of the iris has been reported in 1.5% of patients treated for 12 months with bimatoprost ophthalmic solution 0.03% at the proposed dose of one drop once daily in each affected eye (1.1% of patients treated for 6 months).

Patients should be informed of the possibility of iris colour change. In addition, patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, peribulbar tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.
Mortality and reduced pup body weights were observed when female rats received oral doses was observed at oral doses of bimatoprost which were at least 33 or 97 times, respectively, the formulation or component of the container.

Not recommended for pediatric use. Safety and effectiveness in pediatric patients have not been determined.

Drugs are excreted in human milk, caution should be exercised when LUMIGAN ® RC is administered to nursing mothers.

Hypertrichosis* is the most frequent adverse effect occurring in the eyes in length, thickness, and/or number of eyelashes.

The change in iris colour occurs slowly and may not be noticeable within 2 months of treatment.

No specific drug interaction studies have been conducted. However, no drug-drug interactions are expected.

The data presented below are taken from a randomized, multicentre, double-blind, parallel-group clinical study, of 12 months duration, which was conducted in 650 patients with glaucoma or ocular hypertension. Bimatoprost 0.01% solution was administered once daily and was compared to betaxolol 0.05% and timolol 0.5% ocular solutions administered once daily. Adverse events, regardless of causality, reported from this study are presented in Table 1, below for LUMIGAN ® (bimatoprost) ophthalmic solution 0.01% and LUMIGAN ® (bimatoprost) ophthalmic solution 0.03%.

Table 1: Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients treated with LUMIGAN ® RC (Study 192024-031)

<table>
<thead>
<tr>
<th>50C® Preferred Term</th>
<th>LUMIGAN ® RC (N = 180)</th>
<th>LUMIGAN ® (N = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ocular Events</td>
<td>104 (57.8%)</td>
<td>116 (61.2%)</td>
</tr>
<tr>
<td>Asthenopia</td>
<td>5 (2.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Epiphora</td>
<td>7 (3.9%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>10 (5.5%)</td>
<td>10 (5.3%)</td>
</tr>
<tr>
<td>Glaucous</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Interference</td>
<td>7 (3.9%)</td>
<td>7 (3.8%)</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>10 (5.5%)</td>
<td>10 (5.3%)</td>
</tr>
<tr>
<td>Iris</td>
<td>8 (4.4%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>8 (4.4%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Lash growth</td>
<td>8 (4.4%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Lower eyelid pruritus*</td>
<td>3 (1.6%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Nasal</td>
<td>3 (1.6%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3 (1.6%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Skin</td>
<td>73 (39.0%)</td>
<td>75 (39.0%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>4 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>4 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Xerophthalmia</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

Non-ocular Adverse Events Table 2: Number (%) of Patients with Non-ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients treated with LUMIGAN ® RC (Study 192024-031)

<table>
<thead>
<tr>
<th>50C® Preferred Term</th>
<th>LUMIGAN ® RC (N = 180)</th>
<th>LUMIGAN ® (N = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All non-ocular events</td>
<td>80 (45.2%)</td>
<td>77 (41.2%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>3 (1.6%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>4 (2.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>6 (3.3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2 (1.1%)</td>
<td>10 (5.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.5%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (1.6%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

* Event reported by an investigator as treatment-related at least once in patients for LUMIGAN ® RC.

** Event reported by an investigator as treatment-related at least once in patients for LUMIGAN ® RC.

* Event reported by an investigator as treatment-related at least once in patients for LUMIGAN ® RC.

* Event reported by an investigator as treatment-related at least once in patients for LUMIGAN ® RC.

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Prescribe NEW LUMIGAN® RC for patients with open-angle glaucoma or ocular hypertension.

Demonstrated equivalent mean IOP and fewer overall side effects*
when compared to LUMIGAN® 0.03% †‡

LUMIGAN® RC: a new bimatoprost ophthalmic solution with demonstrated low discontinuation due to adverse events (2.2%)§

Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Bimatoprost ophthalmic solutions have been reported to cause changes to pigmented tissue. The changes included increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). The increased pigmentation may be permanent.¹

The most frequently reported adverse events occurring in approximately 4 to 30% of patients dosed once daily were conjunctival hyperemia (31.4%), growth of eyelashes (3.8%), eye irritation (3.8%) and erythema of eyelid (3.8%).

One drop, once daily in the evening. Please consult prescribing information for complete dosage and administration instructions.¹

Monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised. LUMIGAN® RC has not been studied in patients with severe dry eye, and therefore, should not be used in these patients.¹

* Overall adverse events including all causality and treatment related. The incidence of all causality ocular adverse events was 47.6% vs. 62% for LUMIGAN® RC vs. LUMIGAN® 0.03%, respectively (p<0.005), and all causality non-ocular adverse events was 43.2% vs. 41.2%, respectively.¹
† Randomized, multicentre, double-blind, parallel, 12-month clinical study conducted in patients with open-angle glaucoma or ocular hypertension with a baseline IOP of ≥22 and ≤34 mm Hg, and with no severe dry eye. Patients were given one drop into each affected eye of either bimatoprost 0.01% OD (n=186), bimatoprost 0.0125% OD (n=188) or bimatoprost 0.01% OD (n=187). Results are not shown for bimatoprost 0.0125% OD. The difference in mean IOP between treatment groups was within ± 1.50 mm Hg at all post baseline (17/17) time points, and within ± 1.00 mm Hg at the majority of post baseline time points (9/17), based on 95% CIs.¹
‡ Responder rates, defined as patients (%) achieving a target pressure of <18 mm Hg at every time point, were numerically larger with LUMIGAN® (24.6%) than with LUMIGAN® RC (17.2%), p=0.07.¹
§ Principally conjunctival hyperemia (1.6%), n=185.


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