

Ophthalmics, Glaucoma Agents Review

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Ophthalmics, Glaucoma Agents Review

FDA-Approved Indications

Drug	Manufacturer	Reduction of elevated IOP in ocular hypertension	Reduction of elevated IOP in open-angle glaucoma
Miotics, Topical			
pilocarpine	generic		X
Sympathomimetics			
brimonidine (Alphagan P [®] , generics)	Allergan, generic	X	X
dipivefrin (Propine [®])	generic		X
Beta-blockers			
betaxolol (Betoptic S [®] , generics)	Alcon, generic	X	X
carteolol (Ocupress [®])	generic	X	X
levobunolol (Betagan [®])	generic	X	X
metipranolol (Optipranolol [®])	generic	X	X
timolol (Betimol [®] , generics)	Vistakon, generic	X	X
timolol LA (Istalol [®])	Ista	X	X
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt [®])	Alcon	X	X
dorzolamide (Trusopt [®])	Merck	X	X
Combination Products			
brimonidine/timolol (Combigan [™])	Allergan	X	X
dorzolamide/timolol (Cosopt [®])	Merck	X	X
Prostaglandin Analogs			
bimatoprost (Lumigan)	Allergan	X	X
latanoprost (Xalatan [®])	Pfizer	X	X
travoprost (Travatan [®] , Travatan [®] Z)	Alcon	X	X

Unlike Lumigan and Xalatan, Travatan and Travatan Z are indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension only if patients are intolerant of other intraocular lowering medications or insufficiently responsive to another intraocular pressure lowering agent.

Dorzolamide/timolol (Cosopt) is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers (failed to achieve target IOP determined after multiple measurements over time).

Brimonidine/timolol (Combigan) is indicated for the reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

Overview

Glaucoma is the second most common cause of permanent blindness in the United States and the most common cause of blindness among African-Americans. The prevalence of glaucoma in the United States in adults over 40 years old is estimated to be 1.86 percent.¹ As the American population ages, the prevalence is expected to rise.² African-Americans have a higher prevalence compared to Caucasians; however, whites have a steeper rise in open-angle glaucoma associated with advancing age.^{3,4} Generally, men are more frequently affected by glaucoma.⁵

Increased intraocular pressure (IOP) is common in glaucoma and is believed to contribute to the damage to the optic nerve which can lead to loss of visual sensitivity and field, but it is no longer considered a diagnostic criterion for glaucoma. Two major types of glaucoma have been identified: open-angle and closed-angle. Open-angle glaucoma accounts for the majority of cases. Ocular hypertension may precede glaucoma in some patients. Some of the risk factors for the development of glaucoma include elevated IOP, advancing age, family history of glaucoma, African-American or Hispanic descent, and thinner central corneal thickness.^{6,7,8,9,10}

Reduction of IOP may be accomplished by decreasing the rate of production of aqueous humor or increasing the rate of outflow of aqueous humor from the anterior chamber of the eye.¹¹ Topical ocular hypotensive agents can delay or prevent the development of primary open-angle glaucoma in some patients.¹² In African-Americans with ocular hypertension, the use of topical ocular hypotensive agents has been shown to delay or prevent the onset of primary open-angle glaucoma.¹³

All medications used for the management of glaucoma attempt to limit further damage to the optic nerve. Medication classes used in the management of glaucoma include beta-blockers, miotics, sympathomimetics, topical carbonic anhydrase inhibitors, and prostaglandin analogs. Monotherapy or combination therapy may be used to treat glaucoma and delay the need for surgery and prevent functional vision loss.

Pharmacology

Drug	Decreased Aqueous Humor Production	Increased Trabecular Outflow	Increased Uveoscleral Outflow	Pupil Effect
Miotics, Topical				
pilocarpine (generic)		X		miosis
Sympathomimetics				
brimonidine (Alphagan P, generic)	X		X	miosis ^{14,15}
dipivefrin (Propine, generic)		X	X	mydriasis
Beta-blockers				
betaxolol (Betoptic S)	X			
carteolol (Ocupress, generic)	X			
levobunolol (Betagan, generic)	X			
metipranolol (Optipranolol, generic)	X			
timolol (Betimol, Timoptic, Timoptic XE, Istalol, generic)	X			
Carbonic Anhydrase Inhibitors				
brinzolamide (Azopt)	X			
dorzolamide (Trusopt)	X			
Combination Products				
brimonidine/timolol (Combigan)	X		X	
dorzolamide/timolol (Cosopt)	X			
Prostaglandin Analogs				
bimatoprost (Lumigan)		X	X	
latanoprost (Xalatan)			X	
travoprost (Travatan, Travatan Z)			X	

Pharmacokinetics

Systemic absorption is reported with topical beta-blockers, carbonic anhydrase inhibitors, and topical direct-acting miotics including pilocarpine.^{16,17,18,19} Potential for systemic adverse effects exists for these classes.

Below is a summary of the pharmacokinetics for the prostaglandin analogs.

Drug	Pro-drug	Metabolism	Excretion (%)	Onset (hrs)	Max effect (hrs)
bimatoprost (Lumigan) ²⁰	No	Liver – many metabolites	Urine: 67 Feces: 25	4	8-12
latanoprost (Xalatan) ²¹	Yes - hydrolyzed by esterases to active free acid	Liver – two metabolites	Urine: 88	3-4	8-12
travoprost (Travatan, Travatan Z) ^{22,23}	Yes – hydrolyzed by esterases to active free acid	Liver – inactive metabolites	Rapid systemic elimination	2	After 12

Travatan contains travoprost 0.004% and has benzalkonium chloride 0.015% as the preservative. Travatan Z contains travoprost 0.004% with a different preservative, sofZia™. SofZia contains boric acid, propylene glycol, sorbitol, and zinc chloride. The new preservative, sofZia, is less irritating than benzalkonium chloride.²⁴

Contraindications/Warnings

Dorzolamide/timolol (Cosopt) and brimonidine/timolol (Combigan) are contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of the product.^{25,26}

Beta-blockers are generally contraindicated in patients with sinus bradycardia, second or third degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.^{27,28,29,30,31}

Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Z) are contraindicated in patients with hypersensitivity to the active drug or any of the components.^{32,33,34}

Prostaglandin Analogs^{35,36,37}

All agents in the prostaglandin analog class can cause permanent changes to ocular tissues by increasing pigmentation of the iris and eyelid and growth of eyelashes. Gradual change in eye color to brown may occur due to the increased number of melanosomes in melanocytes. Therapy may need to be discontinued if the increased pigmentation continues. Once discontinued, the pigmentation will not continue to increase, but the resultant color change may be permanent. The long-term effects of this pigmentation change are not known.

Latanoprost (Xalatan) 0.005% once daily has been evaluated for five years for safety and efficacy in patients with primary open-angle or exfoliation glaucoma.³⁸ Enrolled patients initially participated in a three-year, open-label, prospective trial and then entered a two-year extension phase. A total

of 519 patients started the study with 380 patients participating in the two-year extension phase. After five years, iris pigmentation was observed in a small number of patients. For patients with iris pigmentation changes, the onset occurred within the first 24 months in 94 percent of patients. The rate of progression of pigmentation change decreased over time. The mean IOP was reduced by 25 percent from baseline throughout the observation period of five years with 70 percent of patients not requiring a change in therapy.

All agents may gradually change eyelashes by increasing length, thickness, pigmentation, and number of lashes. These changes are especially important when medication is administered to one eye only.

With bimatoprost (Lumigan), onset of iris pigmentation occurs in the first year of therapy for the majority of patients.³⁹ For those who do have iris pigmentation associated with bimatoprost, increasing iris pigmentation has been observed for up to five years. The iris pigmentation did not affect the incidence or severity of other adverse effects. The effects of increased pigmentation beyond five years are not known.

Beta-blockers^{40,41,42,43,44,45,46}

Topically applied ophthalmic beta-blockers have been shown to be systemically absorbed and may produce systemic adverse effects. Adverse effects that have been reported include death due to bronchospasm in patients with asthma and cardiac failure. Beta-blockers can depress the myocardial contractility and result in heart failure in patients with and without a history of cardiac failure.

Caution should be used when prescribing beta-blocker therapy in patients with chronic obstructive pulmonary disease of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease. Using agents other than beta-blockers may be more appropriate for patients with these concurrent disease states. Caution should also be used with beta-blockers in patients with diabetes mellitus as beta-blockers can mask the signs and symptoms of acute hypoglycemia. Beta-blockers may mask certain clinical signs such as tachycardia of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockers that might precipitate a thyroid storm.

Others^{47,48}

Dorzolamide (Trusopt) and brinzolamide (Azopt) are sulfonamides and are absorbed systemically. Severe systemic adverse reactions due to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias are possible. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of dorzolamide.

Pilocarpine is contraindicated in patients with a history of retinal detachment, acute iritis or other conditions which pupillary constriction is contraindicated.⁴⁹

As with all multi-dose ophthalmic products, contamination of the bottle contents may result in infections including bacterial keratitis.

Drug Interactions

Ophthalmic beta-blockers given with oral therapy such as calcium channel blockers, beta blockers, or digitalis may have additive effects in prolonging the atrioventricular conduction time. In patients with impaired cardiac function, use of ophthalmic beta blockers with calcium channel blockers should be avoided.

The use of two beta-blockers for ophthalmic purposes is not recommended.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Ophthalmic products containing thimerosal should be administered at least five minutes apart from latanoprost (Xalatan) as precipitation has been reported.⁵⁰

Adverse Effects

Drug	Blepharitis	Conjunctival Hyperemia	Conjunctivitis (all types)	Dryness	Eyelid Reactions	Foreign Body Sensation	Itching	Ocular Pain	Photophobia	Tearing	Visual Acuity Change	Other
pilocarpine ⁵¹	nr	nr	nr	nr	nr	nr	nr	*	Nr	*	*	
brimonidine 0.15% (Alphagan P) ⁵²	1-4	10-20	10-20	1-4	1-4	1-4	10-20	1-4	1-4	1-4	5-9	5-9 percent: oral dryness
brimonidine 0.2% (Alphagan) ⁵³	3-9	3-30	10-30	3-9	3-9	10-30	10-30	3-9	3-9	3-9	10-30	10-30 percent: oral dryness
brimonidine/timolol (Combigan) ⁵⁴	1-5	5-15	5-15	1-5	1-5	1-5	5-15	5-15	<1	<1	1-5	5-15 percent: conjunctival folliculosis
dipivefrin (Propine) ⁵⁵	nr	6	nr	nr	nr	nr	nr	nr	nr	nr	nr	
betaxolol (Betoptic S) ⁵⁶	nr	*	nr	*	*	*	*	*	*	*	*	
carteolol (Ocupress) ⁵⁷	*	25	*	nr	nr	nr	nr	nr	*	25	*	
levobunolol (Betagan) ⁵⁸	5	nr	5	nr	nr	nr	nr	nr	nr	nr	*	
metipranolol (Optipranolol) ⁵⁹	*	nr	*	nr	*	nr	nr	nr	*	*	*	
timolol (Timoptic) ⁶⁰	*	nr	*	*	nr	nr	*	*	nr	*	*	
timolol gel forming solution (Timoptic XE) ⁶¹	nr	nr	1-5	nr	nr	1-5	1-5	1-5	nr	1-5	*	
timolol LA (Istalol) ⁶²	nr	nr	nr	nr	nr	nr	4-10	nr	nr	nr	4-10	
brinzolamide (Azopt) ⁶³	1-5	nr	nr	1-5	<1	1-5	1-5	1-5		<1	5-10	5-10 percent: bitter taste
dorzolamide (Trusopt) ^{64,65}	nr	1-5	10	1-5	1-5	nr	nr	nr	1-5	1-5	1-5	25 percent: bitter taste;
dorzolamide / timolol (Cosopt) ⁶⁶	1-5	5-15	1-5	1-5	1-5	1-5	5-15	1-5	<1	1-5	5-15	< 30 percent: taste perversion
bimatoprost (Lumigan) ⁶⁷	3-10	15-45	1-3	3-10	3-10	3-10	15-45	3-10	1-3	1-3	3-10	15-45 percent eyelash growth
latanoprost (Xalatan) ⁶⁸	nr	5-15	<1	1-4	1-4	5-15	5-15	1-4	1-4	1-4	5-15	eyelash growth
travoprost (Travatan) ⁶⁹	1-4	35-50	1-4	1-4	1-4	5-10	5-10	5-10	1-4	1-4	5-10	eyelash growth
travoprost (Travatan Z) ⁷⁰	1-4	30-50	1-4	1-4	1-4	5-10	5-10	5-10	1-4	1-4	5-10	eyelash growth

Adverse effects are reported as a percentage. Adverse effects data are obtained from package information and should not be considered comparative.

*= Reported. nr = not reported

In two clinical studies in patients with elevated IOP, brinzolamide (Azopt) 1% was associated with less stinging and burning upon instillation than dorzolamide (Trusopt) 2%.^{71,72}

One report suggests that betaxolol administered as the suspension (Betoptic S) reduces the incidence of stinging upon instillation.⁷³

Systemic reactions to ophthalmic administration of beta-blockers include the following: exacerbation of asthma and COPD, heart failure, arrhythmias including bradycardia, heart block, hypotension, masking signs of hypoglycemia, CNS reactions including depression, and sexual dysfunction.^{74,75,76,77}

Special Populations

Pediatrics

Brimonidine 0.2%, brimonidine/timolol (Combigan) and dorzolamide/timolol (Cosopt) have been studied in well controlled clinical trials involving children ages two years and older.^{78,79,80} Somnolence is the most common adverse effect with brimonidine use and is seen in up to 50 to 83 percent of children ages two to seven years. Older children experienced less somnolence (25 percent) with brimonidine. Dorzolamide (Trusopt) has been studied in a well-controlled pediatric clinical trial of three months duration.^{81,82} The safety and effectiveness of dorzolamide (Trusopt) and timolol have been established when administered individually in pediatric patients aged two years and older. Use of these drug products in these children is supported by evidence from adequate and well-controlled studies in children and adults. Safety and efficacy in pediatric patients below the age of two years have not been established for these two agents. The safety and effectiveness of brimonidine/timolol have been established in the age groups two – 16 years of age. Use of brimonidine/timolol in these age groups is supported by evidence from adequate and well-controlled studies of brimonidine/timolol in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages two to seven years). Brimonidine/timolol is not recommended for use in children under the age of two years.

Safety and IOP-lowering effect of betaxolol (Betoptic S) has been demonstrated in pediatric patients in a three-month, multicenter, double-masked, active-controlled trial.⁸³

For the other products, safety and effectiveness in pediatrics have not been established at this time.

Pregnancy^{84,85,86,87,88,89,90,91,92,93,94,95,96}

Most of the agents used in the treatment of ocular hypertension and glaucoma are Pregnancy Category C. Brimonidine and dipivefrin are the exceptions with Pregnancy Category B classifications.^{97,98}

African-Americans

Travoprost (Travatan) has been shown to provide additional IOP reduction in the African American population compared to other populations.^{99,100}

Severe Renal Impairment

Dorzolamide (Trusopt) has not been studied in severe renal (CrCl less than 30 mL/min) or hepatic impairment.^{101,102} Both dorzolamide (Trusopt) and the metabolite are renally excreted;

therefore, dorzolamide (Trusopt) is not recommended in severe renal impairment. Very little is known about dorzolamide (Trusopt) use in patients with hepatic impairment.

Dosages

Drug	Strength	Dosing	Availability
Miotics, Topical			
pilocarpine solution	0.5, 1, 2, 3, 4, 6%	1 drop up to four times daily	2 mL (1, 2, 4% only), 15 mL
Sympathomimetics			
brimonidine (Alphagan P)	0.1% and 0.15%	1 drop three times daily	5, 10, 15 mL
brimonidine	0.2%	1 drop three times daily	5, 10, 15 mL
dipivefrin (Propine)	0.1%	1 drop twice daily	5, 10, 15 mL
Beta-blockers			
betaxolol (Betoptic S)	0.25%	1-2 drops twice daily	5, 10, 15 mL
carteolol (Ocupress)	1%	1 drop twice daily	5, 10, 15 mL
levobunolol (Betagan)	0.25% and 0.5%	1-2 drops once or twice daily	0.25% - 5, 10 mL 0.5% - 5, 10, 15 mL
metipranolol (Optipranolol)	0.3%	1 drop twice daily	5, 10 mL
timolol solution (Betimol, Timoptic, generic)	0.25% and 0.5%	1 drop twice daily	5, 10, 15 mL
timolol gel forming solution (Timoptic XE, generic)	0.25% and 0.5%	1 drop daily	0.25% - 5 mL 0.5% - 2.5, 5 mL
timolol solution (Istalol)	0.5%	1 drop daily	2.5, 5 mL
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt)	1%	1 drop three times daily	5, 10, 15 mL
dorzolamide (Trusopt)	2%	1 drop three times daily	5, 10 mL
Combination Products			
dorzolamide/timolol (Cosopt)	2% dorzolamide and 0.5% timolol	1 drop twice daily	5, 10 mL
brimonidine/timolol (Combigan)	0.2% brimonidine and 0.5% timolol	1 drop twice daily	5, 10, 15 ml
Prostaglandin Analogs			
bimatoprost (Lumigan)	0.03%	1 drop daily in evening	2.5, 5, 7.5 mL
latanoprost (Xalatan)	0.005%	1 drop daily in evening	2.5 mL 2.5 mL x 3 packages
travoprost (Travatan, Travatan Z)	0.004%	1 drop daily in evening	2.5, 5 mL

When administering other ophthalmic drugs, a period of at least five minutes should elapse before administering one of the prostaglandin analogs.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the studies with patients with elevated IOP are performed in an investigator-masked design. The potential for bias must be considered. Timolol 0.5% is considered the most common comparator in this class.

brimonidine 0.2% and betaxolol suspension (Betoptic S)

Brimonidine 0.2% and betaxolol 0.25% suspension were compared in a multicenter, double-blind trial in 159 patients with elevated IOP.¹⁰³ Patients were randomized to brimonidine or betaxolol twice daily for four weeks. Mean IOP reductions after four weeks were -5.96 mm Hg with brimonidine and -5.07 mm Hg with betaxolol (p=NS). More brimonidine (64.2 percent) patients achieved a reduction of greater than 20 percent in IOP than betaxolol patients (47.4 percent; p=0.033). More patients treated with betaxolol reported hyperemia (p=0.011).

brimonidine (Alphagan, P) and dorzolamide (Trusopt)

A comparison of brimonidine 0.2% and dorzolamide 2% found that the agents reduced IOP to a similar degree.¹⁰⁴ Thirty-eight patients completed the prospective, double-masked, randomized, crossover comparison of brimonidine 0.2% and dorzolamide 2% given three times daily. The mean IOP reduction for both agents was -3 mm Hg (p=0.96) with reductions at hour one and hour three being similar for both agents (p=NS). Dorzolamide was associated with more stinging (p=0.017) and burning (p<0.001) whereas brimonidine was associated with more dry eye complaints (p=0.04).

Brimonidine 0.15% (Alphagan P) and dorzolamide 2% were compared in a randomized, double-blind, multicenter, prospective cross-over trial in 33 patients with open-angle glaucoma or ocular hypertension.¹⁰⁵ Patients underwent a four-week washout period and then were given brimonidine or dorzolamide twice daily for four weeks. Patients underwent a second four-week washout period before switching to the alternate agent. Baseline IOP was similar between the two groups. Reductions in IOP were similar between the two drugs. The trough IOP for both agents after four weeks of therapy was 21 mm Hg (p=0.90). The mean diurnal IOP was 19.3 mm Hg for brimonidine (Alphagan P) and 19.8 mm Hg for dorzolamide. More patients complained of stinging upon instillation with dorzolamide (p=0.02); otherwise, adverse effects were similar between the groups.

brinzolamide (Azopt) and dorzolamide (Trusopt)

In a randomized, placebo-controlled, double-blind study, brinzolamide and dorzolamide were compared for efficacy, safety, and tolerability.¹⁰⁶ Patients were randomized to brinzolamide 1% two or three times daily, dorzolamide 2% three times daily, or placebo given three times daily. A total of 463 patients were randomized with available data for 409 patients for efficacy comparisons. The mean IOP changes after three months of active therapy were -3.4 to -4.1 mm Hg for brinzolamide twice daily, -4.1 to -4.8 mm Hg for brinzolamide three times daily, and -4.3 to -4.9 mm Hg for dorzolamide. All therapies were similar in efficacy in reducing IOP. Burning and stinging upon dose instillation were significantly higher with dorzolamide (12.2 percent) compared to brinzolamide (three percent). Two other studies have confirmed less discomfort with brinzolamide upon dose instillation compared to dorzolamide, however pain may reduce over time with dorzolamide use.^{107,108}

dorzolamide/timolol (Cosopt) and timolol with dorzolamide (Trusopt)

Investigators evaluated the use of the combination product versus the individual components in a two-part study. A total of 131 patients were randomized to dorzolamide/timolol or a topical carbonic anhydrase inhibitor and non-selective beta-blocker.¹⁰⁹ Patients underwent a one-month run-in period using the separate components. At baseline, the mean IOP readings were 18.4 and 21 mm Hg (peak and trough) for the patients randomized to the combination group. The mean IOP at baseline for the individual components were 17.6 and 19.8 mm Hg (peak and trough). After one month of treatment, the peak and trough in the combination groups were 17.6 and 19.5 mm Hg whereas the values were 17.3 and 19 mm Hg in the individual components group. These differences were not statistically significant, indicating that in the clinical trial setting, administering the combination or individual agents provide the same effect on IOP. The other portion of the study enrolled 404 glaucoma patients on individual therapy with a beta-blocker and dorzolamide and converted these patients to the combination therapy. The baseline IOP prior to changing to the combination product was 19.4 mm Hg. After one month of combination therapy in a single container, the IOP was reduced by an additional 1.7 mm Hg ($p < 0.0001$). Of the population, 81 percent of eyes had IOP readings equal to or lower than the baseline readings.

When comparing dorzolamide 2% three times daily and timolol 0.5% twice daily to the combination of dorzolamide 2%/timolol 0.5% given twice daily, the individual products provide slightly greater IOP lowering than the commercially prepared combination when given twice daily per the product labeling.¹¹⁰

timolol and timolol-LA (Istalol)

The newest formulation of timolol maleate (timolol-LA, Istalol) contains potassium sorbate, which enhances the ocular bioavailability of timolol and reduces administration to once daily.¹¹¹ The two formulations were compared to evaluate efficacy and safety in 332 patients with open-angle glaucoma or ocular hypertension.¹¹² In the multicenter, prospective, randomized, double-masked, parallel-group trial, patients were given timolol-LA 0.5% once daily or timolol twice daily for one year. Two hundred ninety patients completed the study. The baseline mean IOP was 25 mm Hg in both groups. At all measurements of IOP, the two groups were similar with a mean post-treatment IOP of 18 to 19 mm Hg at peak drug effect and 19 to 20 mm Hg just prior to redosing. Mean reductions from baseline were 25.5 to 28.7 percent and 20.8 to 24.7 percent for timolol-LA and timolol, respectively. Burning and stinging on instillation, which was mostly described as mild, was reported by 41.6 percent in the timolol-LA group and 22.9 percent with

timolol ($p=0.001$). No patients withdrew due to instillation adverse effects. Discontinuation rates were six percent and 4.2 percent for timolol-LA and timolol, respectively.

brimonidine/timolol (Combigan) and timolol with brimonidine

In two randomized, identical, double-blinded, multicenter trials 1,159 patients with ocular hypertension or glaucoma were treated with fixed brimonidine/timolol twice daily, brimonidine 0.2% three times a day, or timolol 0.5% twice daily for twelve months to evaluate the IOP lowering efficacy and safety of the three products.¹¹³ The mean decrease from baseline IOP during 12-month follow-up was 4.4 to 7.6 mm Hg with fixed brimonidine/timolol, 2.7 to 5.5 mm Hg with brimonidine, and 3.9 to 6.2 mm Hg with timolol. Mean IOP reductions were significantly greater with fixed brimonidine/timolol compared with timolol at all measurements ($p\leq 0.002$) and brimonidine at 8 A.M., 10 A.M., and 3 P.M. ($p<0.001$) but not at 5 P.M. The incidence of adverse events was lower in the fixed-combination group than in the brimonidine group ($p=0.006$) but higher than that in the timolol group ($p<0.001$). The rate of discontinuation for adverse events was 14.3 percent with brimonidine/timolol, 30.6 percent with brimonidine, and 5.1 percent with timolol.

Prostaglandin Analogs

bimatoprost (Lumigan) and latanoprost (Xalatan)

In a study of 64 patients with open-angle glaucoma or ocular hypertension, bimatoprost 0.03%, latanoprost 0.005%, or vehicle given once daily in the evening were compared for safety and efficacy in a 30-day double-blind, randomized trial.¹¹⁴ Baseline IOPs were 22 – 24 mm Hg in all the groups. Both agents significantly lowered IOP from baseline at days 14 and 29. At day 29, bimatoprost (-5.9 to -8 mm Hg) lowered IOP more than latanoprost (-4.4 to -7.6 mm Hg), but the difference was not statistically significant. On day 29, bimatoprost had better diurnal control of IOP than latanoprost. Both agents had similar adverse events and were well tolerated.

In a multicenter, randomized, investigator-blinded three-month trial, latanoprost 0.005% ($n=113$) and bimatoprost 0.03% given once daily ($n=119$); both reduced IOP in patients with ocular hypertension or glaucoma.¹¹⁵ Bimatoprost lowered the IOP at 8 A.M. (12 hours post-dose) to less than 17 mm Hg more frequently than latanoprost (53 versus 43 percent; $p=0.029$). Mean IOP trended to be lower in the bimatoprost group, but the difference did not achieve statistical significance. Conjunctival hyperemia was more common in the bimatoprost group.

Patients were randomized to bimatoprost 0.03% ($n=133$) or latanoprost 0.005% ($n=136$) once daily for six months.¹¹⁶ In the multicenter, investigator-masked study, the mean change from baseline IOP was significantly greater for bimatoprost patients than for latanoprost patients after six months: -1.5 mm Hg greater at 8 A.M. ($p<0.001$), -2.2 mm Hg greater at 12 P.M. ($p<0.001$), and -1.2 mm Hg greater at 4 P.M. ($p=0.004$). The percentages of patients achieving at least 15 percent reduction in IOP from baseline at 8 A.M., 12 P.M., and 4 P.M. at the follow-up visits were 70.7 to 82.1 percent and 48.5 to 61.8 percent for bimatoprost and latanoprost, respectively ($p\leq 0.007$).¹¹⁷ The percentage of patients who achieved at least 20 percent reduction was 57.9 to 68.4 percent for bimatoprost and 36 to 47.1 percent for latanoprost ($p\leq 0.007$). On ophthalmologic examination, conjunctival hyperemia ($p<0.001$) and eyelash growth ($p=0.064$) were more common in bimatoprost patients.

Latanoprost 0.005% and bimatoprost 0.03% given once daily were compared in a double-blind, two-center study with 44 patients.¹¹⁸ Patients underwent a washout period then were randomized to latanoprost or bimatoprost for a seven-week period. After completion, patients

were switched to the alternate treatment without undergoing a washout period. IOP readings were measured at six time points at baseline and after the first and second seven-week treatment periods. Two patients did not complete the study due to conjunctival hyperemia and ocular intolerance; both were associated with bimatoprost therapy. At the end of the treatment periods, mean 24-hour IOP measurements were 17.3 ± 2.8 mm Hg for latanoprost and 16.7 ± 2.4 mm Hg for bimatoprost ($p=0.01$). The largest difference in IOP was at 6 P.M. favoring bimatoprost with IOP (-0.9 mm Hg). Conjunctival hyperemia was more common with bimatoprost ($n=15$) versus latanoprost ($n=six$; $p=0.004$).

A total of sixty patients with normal-tension glaucoma were enrolled in a multicenter, randomized, double-blind clinical trial to compare the IOP-lowering efficacy and safety of bimatoprost 0.03% and latanoprost 0.005%.¹¹⁹ Patients underwent a washout period and then were randomized to daily bimatoprost 0.03% or latanoprost 0.005% for three months. Both active therapies had significant reductions in IOP compared to baseline at all diurnal measurements ($p<0.001$). The morning (8 A.M.) measurement was significantly lower with bimatoprost at two follow-up visits ($p\leq 0.033$). After three months, the mean IOP reductions from baseline were -2.8 to -3.8 mm Hg (17.5 to 21.6 percent) with bimatoprost and -2.1 to -2.6 mm Hg (12.7 to 16.2 percent) for latanoprost. The overall mean reduction in IOP was greater with bimatoprost (-3.4 mm Hg, 19.9 percent) than latanoprost (-2.3 mm Hg, 14.6 percent; $p=0.035$). Adverse effects and clinical success did not differ between the two groups.

bimatoprost (Lumigan), latanoprost (Xalatan), and timolol gel-forming solution

In the randomized, multicenter, investigator-masked, prospective study, bimatoprost, latanoprost, and timolol gel-forming solution were compared for efficacy and safety in patients with ocular hypertension or open-angle glaucoma.¹²⁰ After a washout period, patients were randomized to bimatoprost 0.03% daily in the evening ($n=38$), latanoprost 0.005% daily in the evening ($n=38$), or timolol maleate 0.5% gel-forming solution daily in the morning ($n=39$) for one month. Measurements of IOP were taken at eight time points during the 24 hours on day 28. At peak drug effect (10 A.M.), mean IOP reduction from baseline was significantly greater with bimatoprost (-9.3 mm Hg, -40.3 percent) than with timolol gel (-7.1 mm Hg, -31.1 percent; $p=0.024$) or latanoprost (-7.4 mm Hg, -33.3 percent). The mean overall IOP was significantly lower with bimatoprost (15.1 ± 0.6 mm Hg) or latanoprost (15.7 ± 0.4 mm Hg) than with timolol gel (17.4 ± 0.6 mm Hg; $p<0.001$). Conjunctival hyperemia occurred more frequently with bimatoprost (39.5 percent) compared to latanoprost (15.8 percent) and timolol (2.6 percent).

bimatoprost (Lumigan) and travoprost (Travatan)

Bimatoprost 0.03% and travoprost 0.004% were evaluated in 31 African-American patients with glaucoma or ocular hypertension in an investigator-blinded, multicenter trial over three months.¹²¹ After a washout period, patients were randomized to bimatoprost or travoprost once daily. Both agents reduced IOP similarly, but bimatoprost more frequently achieved the target pressure of 12 to 19 mm Hg after three months of therapy. The mean IOP reduction from baseline was -8.4 mm Hg with bimatoprost and -7.9 mm Hg with travoprost.

In a larger trial by the same lead investigator, bimatoprost 0.03% was compared to travoprost 0.004% in 94 black patients with open-angle glaucoma or ocular hypertension over three months.¹²² Each therapy was given once daily for three months in a multicenter, randomized, investigator-blinded study. Both therapies significantly lowered IOP at all study visits ($p<0.001$). Mean IOP reductions from baseline were -6.8 to -7.8 mm Hg (27 to 31 percent) for bimatoprost and -6.2 to -6.9 mm Hg (25 to 28 percent) for travoprost. By the end of the study, 85 and 68 percent of patients receiving bimatoprost and travoprost, respectively, achieved at least a 20

percent mean reduction of IOP. Patients with mean IOP reductions of at least 40 percent were reported in 31.9 and 20.9 percent for the bimatoprost and travoprost groups, respectively. Ocular redness was the most commonly reported adverse drug reaction in both groups.

Another small comparative trial evaluated bimatoprost 0.03% and travoprost 0.004% in 26 patients with glaucoma or ocular hypertension over six months.¹²³ The study was a randomized, investigator-blinded, parallel-group trial. Patients underwent a washout period and then were randomized. Baseline IOP was similar between the groups. Both agents after six months reduced IOP significantly from baseline with mean IOP reductions of -7.4 to -8.8 mm Hg (-34 to -36 percent) with bimatoprost and -4.6 to -7.2 mm Hg (-19 to -29 percent) with travoprost ($p \geq 0.057$). More bimatoprost patients achieved target IOP than those in the travoprost group. Ocular hyperemia was the most common adverse event reported in both groups. Further study is planned.

In a randomized, investigator-blinded, parallel-group trial, 157 patients with glaucoma or ocular hypertension were enrolled to compare the IOP-lowering effects of bimatoprost 0.03% and travoprost 0.004% over six months.¹²⁴ Five study visits recorded IOP at three time points (9 A.M., 1 P.M., and 4 P.M.) and found no significant differences between the two treatment groups. Both drugs significantly lowered IOP at all time points ($p \leq 0.001$). The only time point with a significant difference between the therapies was at 9 A.M., when mean IOP reduction was 7.1 mm Hg (27.9 percent) for bimatoprost and 5.7 mm Hg (23.3 percent) with travoprost ($p = 0.014$). Ocular redness was the most common adverse effect.

bimatoprost (Lumigan) and timolol

A number of multicenter, double-blind trials have been done to compare the safety, tolerability, and efficacy of bimatoprost 0.03% instilled once or twice daily with timolol 0.5% instilled twice daily in patients with ocular hypertension or glaucoma.

After three months of therapy, the mean reduction in IOP from baseline was -9.16 mm Hg (-35.2 percent) with bimatoprost once daily, -7.78 mm Hg (-30.4 percent) with bimatoprost 0.03% twice daily, and -6.74 mm Hg (-26.2 percent) with timolol twice daily in a group of 596 patients who were randomized in a double-masked manner.¹²⁵ At all measurements, mean IOP reductions were significantly greater in the bimatoprost once daily group than in the timolol group, and the IOP lowering provided by bimatoprost daily was sustained for at least six months.¹²⁶ After one year of therapy, bimatoprost daily lowered IOP measurements below 17 mm Hg in 58 percent of patients compared to 37 percent of the timolol patients ($p = 0.001$).¹²⁷ Bimatoprost daily provided significantly greater mean reductions in IOP from baseline than timolol after two years of therapy ($p \leq 0.001$).¹²⁸ Bimatoprost daily was also shown to have greater reductions in mean IOP versus timolol over the two-year period ($p < 0.006$). Twice daily dosing of bimatoprost also provided significantly greater mean reductions in IOP than timolol but was not as effective as once daily dosing. Bimatoprost was associated with significantly more hyperemia and eyelash growth than timolol, whereas timolol was associated with significantly more burning and stinging sensation in eyes. Overall, bimatoprost was well tolerated with few discontinuations due to adverse events.

bimatoprost (Lumigan) and dorzolamide/timolol (Cosopt)

In a multicenter, double-blind study, 177 patients with glaucoma or ocular hypertension who were not controlled after at least two weeks of timolol maleate 0.5% were randomized to bimatoprost 0.03% once daily or combined dorzolamide 2%/timolol 0.5% twice daily for three months.¹²⁹ Bimatoprost provided significantly greater IOP-lowering effects and better diurnal

control than dorzolamide/timolol. At the 8 A.M. measurements, bimatoprost lowered mean IOP -6.8 to -7.6 mm Hg from baseline, whereas combined timolol and dorzolamide lowered mean IOP -4.4 to -5 mm Hg from baseline ($p < 0.001$). More patients achieved 8 A.M. IOP measurements less than 16 mm Hg with bimatoprost. In the dorzolamide/timolol group, taste perversion, ocular burning, and stinging with instillation occurred more frequently. Conjunctival hyperemia was more commonly reported with bimatoprost.

latanoprost (Xalatan) and brimonidine (Alphagan)

Patients with uncontrolled glaucoma or ocular hypertension on beta-blockers were enrolled in a trial comparing brimonidine 0.2% twice daily and latanoprost 0.005% daily as adjunctive therapy over three months.¹³⁰ In the prospective, multicenter, double-blind trial, 115 patients with baseline IOP of 21.3 mm Hg while on beta-blocker therapy were randomized. After one month of therapy, if at least 15 percent reduction in IOP at peak effect was not achieved, patients were switched to the alternative therapy. Response rates (at least 15 percent reduction in IOP) and IOP reduction were similar between brimonidine and latanoprost at one month. Of the patients with successful IOP reduction at one month, the three-month mean IOP reductions were similar (-4.55 mm Hg reduction of IOP for brimonidine and -5.49 mm Hg reduction for latanoprost). Significantly more patients on latanoprost complained of watery or teary eyes ($p = 0.025$) and cold extremities ($p = 0.012$).

Brimonidine 0.2% twice daily and latanoprost 0.005% once daily were compared in 127 patients with open-angle glaucoma or ocular hypertension in a randomized, three-month, multicenter, double-blind trial.¹³¹ The mean IOP after the medication washout period was 24.1 and 24.5 mm Hg in the latanoprost and brimonidine groups, respectively. Patients who had previously been treated with either agent were excluded from the study. Eighty percent of the brimonidine group and 74 percent of the latanoprost group achieved at least 20 percent reduction in IOP compared to baseline. The mean IOP reduction from baseline in each group at month three was -6.8 mm Hg with brimonidine and -6.5 mm Hg with latanoprost. More treatment-naïve patients treated with brimonidine achieved at least 20 percent decrease in IOP versus latanoprost (88 versus 59 percent; $p = 0.01$). The previously treated patients achieved at least 20 percent reduction in IOP more frequently with latanoprost than brimonidine (88 versus 74 percent; $p = \text{NS}$).

latanoprost (Xalatan) and dorzolamide/timolol (Cosopt)

Two three-month, randomized, double-blinded trials compared efficacy of dorzolamide 2%/timolol 0.5% twice daily and latanoprost 0.005% once daily in patients with ocular hypertension or open-angle glaucoma.¹³² Study A had 256 patients from the U.S., and Study B had 288 patients from Europe and Israel. Patients underwent a washout period and then were required to have baseline IOP greater than 24 mm Hg for study eligibility. Measurements of IOP occurred at 8 A.M., 10 A.M., 2 P.M., and 4 P.M.. After three months, the mean daytime diurnal IOP was 18.9 mm Hg for the dorzolamide/timolol combination versus 18.4 mm Hg for latanoprost in Study A, and 17.4 mm Hg for the dorzolamide/timolol combination versus 17.5 mm Hg for latanoprost in Study B. Both therapies were well tolerated with only ocular stinging reported more frequently with dorzolamide/timolol. In a post-hoc analysis, both agents achieved a 40 percent reduction in IOP (target level) in 15 percent of the dorzolamide/timolol and 13 percent of the latanoprost groups.¹³³ In the patients with high baseline IOP (> 30 mm Hg), the mean IOP reduction was also similar (dorzolamide/timolol 12.5 mm Hg; latanoprost 12.6 mm Hg).

travoprost (Travatan) and brinzolamide (Azopt) or timolol

The efficacy and safety of timolol 0.5% and brinzolamide 1% when given in combination with travoprost 0.004% were compared in 192 patients with ocular hypertension or primary open-angle glaucoma.¹³⁴ In the double-blind, randomized parallel study, patients were started on travoprost every evening for four weeks and then were randomized to timolol or brinzolamide given twice daily. IOP measurements were recorded at the end of travoprost monotherapy and then 12 weeks after receiving the combination therapy. There were no differences between the groups for IOP reductions from baseline, each time point of IOP measurement throughout the day or for the mean diurnal IOP (18.1 mm Hg for both groups). No significant differences were observed for adverse effects either, with the most common adverse effects being conjunctival hyperemia (16 percent) with brinzolamide- and six percent with timolol-treated patients (p=0.06).

travoprost (Travatan) and dorzolamide/timolol (Cosopt)

Travoprost 0.004% and dorzolamide 2%/timolol 0.5% were compared in randomized, single-blind study enrolling 56 patients with ocular hypertension or open-angle glaucoma over six weeks of therapy.¹³⁵ The dorzolamide/timolol group received twice daily therapy, and the travoprost group received therapy once daily at 9 P.M. Most of the patients had brown eyes and had a diagnosis of open-angle glaucoma. Blacks accounted for 79.3 percent of the travoprost group and 59.3 percent of the combination group. Baseline IOP readings and other patient demographics were similar between the groups. The mean IOP reductions from baseline were -7.1 mm Hg (-30.7 percent) for travoprost and -4.5 mm Hg (-21.7 percent) for dorzolamide/timolol group after six weeks of therapy. Travoprost was observed to have significantly lower IOP readings at 8 A.M., 12 P.M., 4 P.M., and 8 P.M. (all time points) compared to the combination group (p<0.01). Taste perversion was more common in the dorzolamide/timolol group.

travoprost (Travatan) and timolol

A total of 426 patients who had open-angle glaucoma or ocular hypertension and were inadequately controlled on timolol 0.5% twice daily were randomized in a double-masked trial to receive travoprost 0.0015% or 0.004% or placebo in the evening.¹³⁶ Patients were followed for six months. The IOP was lowered an additional -5.7 to -7.2 mm Hg and -5.1 to -6.7 mm Hg in the travoprost 0.004% and 0.0015% concentrations, respectively. These changes were significantly different from the vehicle group (-1.3 to -2.8 mm Hg, p≤0.0001). Average hyperemia scores ranged from trace to mild for all treatment groups.

Two double-blind, randomized studies, one six-month (n=605) and one nine-month (n=573), evaluated travoprost 0.0015% and 0.004% once daily with timolol 0.5% twice daily in patients with open-angle glaucoma or ocular hypertension.^{137,138} Enrollment required baseline IOP between 24 and 36 mm Hg in at least one eye. Travoprost 0.0015% and 0.004% significantly lowered mean IOP measurements more than timolol in both studies. In the nine-month study, travoprost 0.004% produced a significantly greater reduction in the mean IOP than timolol (-8 to -8.9 mm Hg versus -3.6 to -7.9 mm Hg; p≤0.00001) compared to baseline. Hyperemia was more common with travoprost. In the six-month study, 29.2 percent of travoprost 0.0015% patients experienced hyperemia compared to 42.8 percent of travoprost 0.004% and 8.9 percent of timolol patients. In the nine-month study, timolol was better tolerated than either strength of travoprost.

travoprost (Travatan), latanoprost (Xalatan), and timolol

A total of 801 patients with open-angle glaucoma or ocular hypertension were randomized in a double-masked trial to receive travoprost 0.0015%, 0.004%, latanoprost 0.005%, or timolol 0.5% for a period of 12 months.¹³⁹ Patients receiving travoprost or latanoprost received once daily administrations; patients receiving timolol had twice daily administrations. Travoprost was equal or superior to latanoprost and superior to timolol with mean IOP over visits and time of day ranging from 17.9 to 19.1 mm Hg (travoprost 0.0015%), 17.7 to 19.1 mm Hg (travoprost 0.004%), 18.5 to 19.2 mm Hg (latanoprost), and 19.4 to 20.3 mm Hg (timolol). Travoprost was associated with good reductions in IOP in the black population. Response rate, considered to be at least 30 percent or greater IOP reduction from diurnal baseline or IOP 17 mm Hg or less, was 49.3 and 54.7 percent for travoprost 0.0015% and 0.004%, respectively, compared with 49.6 percent for latanoprost and 39 percent for timolol. Iris pigmentation change was observed in five percent of patients receiving travoprost 0.0015%, 3.1 percent of patients receiving travoprost 0.004%, 5.2 percent of patients receiving latanoprost, and none of the patients receiving timolol.

In two double-blind, randomized studies with a total of 1,381 black and nonblack patients with open-angle glaucoma or ocular hypertension, travoprost, latanoprost, and timolol were evaluated for efficacy.¹⁴⁰ Patients were randomized to travoprost 0.004% daily, latanoprost 0.005% daily, or timolol 0.5% twice daily. The mean IOP was significantly lower in blacks treated with travoprost, and travoprost was superior to latanoprost in blacks. Timolol lowered the mean IOP to a greater extent in nonblack patients.

travoprost (Travatan), latanoprost (Xalatan), and bimatoprost (Lumigan)

Travoprost 0.004%, bimatoprost 0.03%, and latanoprost 0.005% daily were compared for efficacy, safety, and tolerability over 12 weeks with 411 patients with open-angle glaucoma or ocular hypertension.¹⁴¹ The study was a multicenter, double-blind, randomized clinical trial based in the US. Baseline IOP after washout was at least 23 mm Hg in one or both eyes. Patients were randomized to one of the three therapies and followed for reduction in IOP and hyperemia. After 12 weeks, IOP was measured at 8 A.M., 12 P.M., 4 P.M., and 8 P.M. IOP readings were similar at all time points for all drugs (16-17.6 mm Hg). Latanoprost patients reported fewer ocular adverse effects compared to bimatoprost. Average hyperemia scores were lower with latanoprost compared to bimatoprost (p=0.001).

A study enrolled 44 patients with glaucoma or ocular hypertension in a randomized, double-blind crossover study comparing the effects of latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% on the circadian IOP.¹⁴² Patients were treated with each agent for one month, each given in a random sequence with a 30-day washout period between drugs. IOP was recorded at eight time points in a 24-hour period at baseline and following treatment with each agent. All three agents significantly reduced IOP compared to baseline. The mean IOP reductions were similar among the agents with no significant differences. All agents tested had greater effect during the daytime than at night.

travoprost (Travatan) and travoprost (Travatan Z)

The safety and efficacy of travoprost 0.004% without benzalkonium chloride (BAC) and travoprost 0.004% (Travatan) were compared in 790 patients with open-angle glaucoma or ocular hypertension.¹⁴³ In the double-blinded, randomized, parallel group trial adult patients received one of the formulations of travoprost as one drop once daily. IOP measurements at 8 A.M., 10 A.M., and 4 P.M. were taken at three visits over three months. Mean IOP reductions,

across all study visits and times ranged from 7.3 to 8.5 mm Hg for travoprost 0.004% without BAC and from 7.4 to 8.4 mm Hg for travoprost 0.004% with BAC (p=NS). Adverse events were similar between the two groups with the exception of hyperemia which occurred in 6.4 percent with travoprost without BAC and 9 percent in travoprost (Travatan).

Summary of IOP Reduction of Prostaglandin Analogs

Drug	Baseline IOP (mm Hg)	Reduction in IOP (mm Hg)
bimatoprost (Lumigan) ¹⁴⁴	26	7-8
latanoprost (Xalatan) ¹⁴⁵	24-25	6-8
travoprost (Travatan, Travatan Z) ^{146,147}	25-27	7-8 (more in African-American patients)

Above data are from the package inserts and are not meant to be comparative.

Meta-Analyses

A meta-analysis evaluated nine studies of the prostaglandin analogs for the management of glaucoma or ocular hypertension.¹⁴⁸ A total of 1,318 patients were evaluated in this analysis. Patients treated with travoprost and bimatoprost had lower IOP levels at the end of follow-up (-0.98 mmHg [95% CI: -2.08; 0.13; p=0.08] and -1.04 mmHg [95% CI: -2.11;0.04; p=0.06], respectively) than those treated with latanoprost. In another meta-analysis, travoprost 0.004% had equivalent efficacy to bimatoprost and latanoprost in a total of 12 studies. Travoprost had greater efficacy in reducing IOP than timolol.¹⁴⁹

A meta-analysis evaluated the IOP reduction of several agents in this class.¹⁵⁰ A total of 27 articles with 6,953 patients with trough IOP readings and 6,841 patients with peak IOP readings were included. Over 85 percent of patients had primary open-angle glaucoma or ocular hypertension. The greatest IOP reductions were reported with timolol, latanoprost, travoprost, and bimatoprost, with peak reductions of 27 to 33 percent and trough reductions of 26 to 29 percent from baseline.

Summary

Selection of a wide variety of agents for the treatment of glaucoma is important, as patients often require a combination of therapies to achieve adequate control of elevated IOP. Currently, no guidelines suggest any one class should be used as first line; however, safety and tolerability of the medications should play a role in product selection.^{151,152} The target IOP reductions are typically 20 to 30 percent, and even up to 50 percent below baseline. Beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs are the mainstays of therapy. Direct-acting miotics including pilocarpine are second or third line therapy now due to frequent administration and lower tolerability. Adequate treatment of glaucoma requires a high level of adherence to therapy for treatment success.¹⁵³

Most head-to-head comparative studies have been performed in small patient populations. Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) have been shown to have better efficacy compared to timolol. The prostaglandin analogs have also been shown to have an additive effect when used with beta-blocker therapy. Side effect profiles of the prostaglandin analogs are different than the beta-blocker agents used for glaucoma treatment.

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