Therapeutic Class Overview
Ophthalmic Prostaglandin Analogues

Therapeutic Class

- **Overview/Summary:** The four ophthalmic prostaglandin analogues approved by the Food and Drug Administration (FDA) for the treatment of glaucoma are bimatoprost (Lumigan®), latanoprost (Xalatan®), tafluprost (Zioptan®) and travoprost (Travatan Z®). They reduce intraocular pressure (IOP) by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.[1-5] Evidence shows that reducing IOP inhibits the progression of optic nerve damage and visual field loss.[6-7] An IOP of greater than 22 mm Hg is typically considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression. The various classes of medication used in the medical management of glaucoma include alpha$_2$-adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics and prostaglandin analogues. Tafluprost, the newest prostaglandin analogue to be approved by the FDA, is the only agent in the class that is formulated as preservative-free. Travoprost contains the preservative sofZia, which may be less irritating/allergenic to the ocular surface compared to benzalkonium chloride (BAK), used in bimatoprost and latanoprost formulations. The BAK-containing travoprost formulation (Travatan) was discontinued by the manufacturer in June 2010. Latanoprost is the only prostaglandin analogue that is currently available generically. The most frequently reported adverse events associated with the prostaglandin analogues include burning/stinging, hyperemia, pruritus, iris pigmentation changes and growth and darkening of eyelashes.[1-5] All of the ophthalmic prostaglandin analogues have been shown to reduce IOP from baseline by ≥30%.[8]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bimatoprost (Lumigan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.01% (2.5, 5, 7.5 mL) 0.03% (2.5, 5, 7.5 mL)	-
Latanoprost (Xalatan®*)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.005% (2.5 mL)	✔
Tafluprost (Zioptan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.0015% (30 or 90 0.3 mL single-use containers)	-
Travoprost (Travatan Z®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.004% (2.5, 5 mL)	-

*Available generically in one dosage form or strength.

Evidence-based Medicine

- In one study (N=38) the reduction in intraocular pressure (IOP) from baseline did not differ significantly between patients receiving tafluprost or latanoprost over six weeks (difference, 0.170 mm Hg; 95% confidence interval [CI], -1.268 to 1.608; *P*=0.811).[9] In a six-week study with a crossover design travoprost was associated with a greater reduction in IOP from baseline compared to tafluprost (7.2 vs 6.6 mm Hg; *P*=0.01); however, adverse events and tolerability were similar between the treatment groups.[10]
- In a randomized, double-blind study (N=533), tafluprost was noninferior to latanoprost treatment after 24 months, with no differences in adverse events reported between the two groups (*P*<0.05).[11] In a noninterventional study of patients with ocular intolerance to latanoprost, a significantly lower incidence of eye irritation/burning, tearing, itching, dry eye sensation and conjunctival hyperaemia

was reported after switching to tafluprost therapy (*P*<0.001 for all). Tafluprost also significantly lowered IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mm Hg; *P*=0.049).[12]

- The results of a meta-analysis demonstrated that reductions in IOP were greater with bimatoprost 0.03% compared to travoprost at 8 AM (*P*=0.004) and 12 noon (*P*=0.02), but not at 4 PM (*P*=0.190) or 9 PM (*P*=0.070).[13] In another meta-analysis, bimatoprost was associated with the greatest reduction in IOP (33%; 95% CI, 31 to 35) followed by latanoprost (31%; 95% CI, 29 to 33) and travoprost (31%; 95% CI, 29 to 32).[14] In a study evaluating bimatoprost 0.03%, latanoprost and travoprost, the mean changes in IOP were comparable between all treatment groups by week 12 (*P*=0.128); however, latanoprost was associated with fewer adverse events compared to bimatoprost (*P*<0.001).[15]
- The results of a systematic review show that the prostaglandin analogues are associated with a greater percentage reduction in IOP from baseline compared to timolol after six months (-28.6 vs -22.2%; *P* value not reported). Prostaglandin analogues reduced IOP further than timolol at one (-27.2 vs -21.2%; *P* value not reported) and three months (-28.8 vs -22.2%; *P* value not reported).[16]
- In a randomized controlled study, latanoprost was associated with greater reductions in IOP compared to betaxolol, carteolol and nipradilol *(P*<0.05)*.*[17] Moreover, a meta-analysis of 11 randomized control trials showed significant reductions in IOP with latanoprost compared to timolol *(P*<0.001)*.*[18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Patients with ocular hypertension or suspected open-angle glaucoma should be offered medication based on the risk factors of measured intraocular pressure (IOP), measured central corneal thickness and age.[19]
    - Ophthalmic formulations of β adrenergic antagonists and prostaglandin analogues are most frequently used to lower IOP. Prostaglandin analogues are the most effective IOP-lowering drugs and can be considered as initial medical therapy.[20]
    - Ophthalmic prostaglandin analogues should be offered to new patients diagnosed with early or moderate open-angle glaucoma at risk of significant vision loss and patients with advanced open-angle glaucoma who are scheduled for surgery. Pharmacological treatment for elevated IOP should continue until progression of optic nerve head damage, progression of visual field defect or reported intolerance to current medication.[19]
    - Pharmacological treatment should be switched to another class (ophthalmic β adrenergic antagonist, alpha$_2$-adrenergic agonist, carbonic anhydrase inhibitor or sympathomimetic) when medication intolerance to current medication is experienced or IOP reduction has not been achieved.[8,19-20]

- Other Key Facts:
    - Latanoprost is the only ophthalmic prostaglandin analogue that is available generically.[5]
    - Tafluprost is the only preservative-free ophthalmic prostaglandin product and is only available in single-use containers.[5]
    - Bimatoprost and latanoprost are formulated with benzalkonium chloride, an agent associated with ocular irritation/inflammation in some patients. Travoprost is formulated with sofZia, an ionic buffer containing borate, sorbitol, propylene glycol, and zinc.[1-4]

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Therapeutic Class Review
Ophthalmic Prostaglandin Analogues

Overview/Summary

Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world.[1] Four distinct types of glaucoma include primary open-angle, acute angle-closure, secondary and congenital. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma or a central corneal thickness of less than 545 micrometers.[2-3] Other possible risk factors that have been investigated include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus and hypothyroidism.[1,3-6]

IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage.[1-3,7] Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP greater than 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression.[7] The target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[2,3]

The current treatment of glaucoma focuses on decreasing IOP by one of three methods: laser therapy, surgery or medical intervention.[1-3] Medical intervention is generally used as initial therapy prior to laser or surgical treatment. Medical intervention includes five classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-$_2$ adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics and prostaglandin analogues. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow.[7] Parasympathomimetics and prostaglandin analogues increase aqueous outflow, while β adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha-$_2$ adrenergic agonists both decrease the amount of aqueous humor formed and increase its outflow.[7] Current guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents.[2,3,8]

This class review consists of the ophthalmic prostaglandin analogues, which include bimatoprost (Lumigan®), latanoprost (Xalatan®), tafluprost (Zioptan®) and travoprost (Travatan Z®).[9-12] The ophthalmic prostaglandin analogues are approved by the Food and Drug Administration (FDA) to reduce IOP in patients with open-angle glaucoma or ocular hypertension. These agents reduce IOP by increasing the outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.[9-12] All of the ophthalmic prostaglandin analogues are administered once daily. Ophthalmic tafluprost is the only agent in the class that is formulated as preservative-free. Ophthalmic travoprost contains the preservative sofZia®, which may be less irritating/allergenic to the ocular surface compared to benzalkonium chloride, which is used in ophthalmic bimatoprost and latanoprost formulations. The benzalkonium chloride-containing travoprost formulation (Travatan®) was discontinued by the manufacturer in June 2010. Bimatoprost is the only ophthalmic prostaglandin analogue that is available in multiple strengths (0.01 and 0.03% solution). Ophthalmic latanoprost is currently available generically.[13] The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes and growth and darkening of eyelashes.[9-12,14,15] The ophthalmic prostaglandin analogues are the most effective drugs in lowering IOP. The results of meta-analyses have demonstrated a reduction in IOP of 28 to 33% and flatter 24-hour IOP curve, resulting in

less fluctuation in IOP pressures with the prostaglandin analogues compared to β adrenergic antagonists and other agents used in the management of glaucoma.[16]

Table 1. Medications Included Within Class Review[9-12]

Generic Name (Trade name)	Medication Class	Generic Availability
Bimatoprost (Lumigan®)	Prostaglandin analogue	-
Latanoprost (Xalatan®*)	Prostaglandin analogue	✔
Tafluprost (Zioptan®)	Prostaglandin analogue	-
Travoprost (Travatan Z®)	Prostaglandin analogue	-

*Available generically in one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[9-12]

Indication	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	✔	✔	✔	✔

Pharmacokinetics

Table 3. Pharmacokinetics[9-12,14,15]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (minutes)
Bimatoprost	Low	Not reported	~67	Not reported	45
Latanoprost	Not reported	Not reported	~88	Latanoprost acid	17
Tafluprost	Not reported	Not reported	Not reported	Tafluprost acid	30
Travoprost	Not reported	Not reported	<2	Travoprost acid	45

Clinical Trials

Clinical trials evaluating the safety and efficacy of the ophthalmic prostaglandin analogues for the reduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension are described in Table 4.[16-54]

Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between ophthalmic travoprost and ophthalmic latanoprost.[16,18,19,23,26,28,29,33,34] Available trials suggest that ophthalmic tafluprost may have a similar IOP-lowering effect as ophthalmic latanoprost but less than ophthalmic travoprost.[47-50] In one trial, there was no significant difference in IOP reduction from baseline between ophthalmic tafluprost and ophthalmic travoprost following six weeks of treatment (difference, 0.170 mm Hg; 95% confidence interval [CI] -1.268 to 1.608; *P*=0.811).[47] In a six-week crossover trial, ophthalmic travoprost significantly reduced IOP from baseline compared to ophthalmic tafluprost (7.2 vs 6.6 mm Hg; *P*=0.01). Adverse events were similar between the treatment groups.[50] In a randomized, double-blind trial (N=533), ophthalmic tafluprost demonstrated non inferiority to ophthalmic latanoprost treatment after 24 months (*P*<0.05). No difference in the incidence of adverse events was reported between treatments.[49] In a noninterventional trial by Erb and colleagues, patients with an inadequate response with prior glaucoma treatments achieved a significantly lower IOP after switching to ophthalmic tafluprost treatment for six to 12 weeks compared to baseline (16.4±2.9 vs 19.5±4.4 mm Hg; *P*<0.001).[45] Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation and conjunctival hyperemia when switched from ophthalmic latanoprost to ophthalmic tafluprost due to ocular intolerance (*P*<0.001 for all). Ophthalmic tafluprost also significantly reduced IOP compared to baseline treatment with ophthalmic latanoprost (16.4 vs 16.8 mm Hg; *P*=0.049).[46]

In a trial comparing ophthalmic bimatoprost 0.03% and ophthalmic travoprost, the mean reduction in IOP was significantly greater with ophthalmic bimatoprost 0.03% at 9 AM (P<0.014), but not at 1 PM (P=0.213) or 4 PM (P≥0.207).[19] The results of a meta-analysis demonstrated that reductions in IOP were significantly greater with ophthalmic bimatoprost 0.03% compared to ophthalmic travoprost at 8 AM (P=0.004) and 12 noon (P=0.02), but not at 4 PM (P=0.190) or 9 PM (P=0.070). Ophthalmic bimatoprost 0.03% also demonstrated greater reductions in IOP compared to ophthalmic latanoprost at all time points. There were no statistically significant differences between ophthalmic latanoprost and ophthalmic travoprost at any time point.[28] In a trial evaluating ophthalmic bimatoprost 0.03%, ophthalmic latanoprost and ophthalmic travoprost, the mean changes in IOP were comparable between all treatment groups at week 12 (P=0.128); however, ophthalmic latanoprost was associated with fewer adverse events compared to ophthalmic bimatoprost (P<0.001).[26] In a meta-analysis of peak and trough IOP measurements, ophthalmic bimatoprost 0.03% demonstrated greater reductions in peak IOP compared to ophthalmic latanoprost; however, reductions were larger with ophthalmic latanoprost at the trough measurement.[34] Results from a similar meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between ophthalmic bimatoprost 0.03% and ophthalmic travoprost (P=0.80) or ophthalmic latanoprost and ophthalmic travoprost (P=0.07).[33]

In a randomized controlled trial, treatment with ophthalmic latanoprost was associated with greater reductions in IOP compared to ophthalmic betaxolol, ophthalmic carteolol and ophthalmic nipradilol (P<0.05 for all).[44] In addition, a meta-analysis of 11 randomized control trials showed significant reductions in IOP with ophthalmic latanoprost compared to ophthalmic timolol (P<0.001).[36] The ophthalmic prostaglandin analogues have consistently shown greater efficacy in reducing IOP compared to agents in other ophthalmic classes used as monotherapy.[26,36,41] Only ophthalmic brimonidine reduced IOP to a similar degree as ophthalmic prostaglandin analogue monotherapy (P=0.30 vs ophthalmic latanoprost) but with a higher incidence of adverse events (31 vs 21%; P=0.0005).[42] The results from a meta-analysis by Cheng et al demonstrate that ophthalmic brimonidine had the largest reduction in IOP at peak compared to all other glaucoma agents; however, ophthalmic brimonidine also had the smallest reduction in IOP at the trough timepoint.[34]

The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to combination therapy.[31,32,37-40] Ophthalmic bimatoprost 0.03% significantly reduced IOP compared to ophthalmic dorzolamide/timolol in a six-week crossover trial (P=0.03).[31] In a meta-analysis of 14 trials, treatment with ophthalmic latanoprost or fixed-dose ophthalmic dorzolamide/timolol was associated with a similar reduction in IOP after six months (P=0.28).[40]

A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that ophthalmic latanoprost had a lower incidence of conjunctival hyperemia compared to both ophthalmic bimatoprost 0.03% and ophthalmic travoprost (P<0.0001 for both).[52] Moreover, one trial evaluating the effect of ophthalmic latanoprost compared to placebo on asthmatic patients showed no change in peak expiratory flow volume in the morning (P=0.76) or at night (P=0.12).[53] One trial evaluated the use of ophthalmic travoprost without the preservative benzalkonium chloride (BAK) and demonstrated a lower incidence of hyperemia compared to travoprost with BAK (P values not reported).[54] The results from a second trial showed that ophthalmic travoprost without BAK was associated with lower Ocular Surface Disease Index scores compared to ophthalmic bimatoprost 0.03% and latanoprost (P<0.0001).[55]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Reduction of Intraocular Pressure in Patients with Open-angle Glaucoma or Ocular Hypertension				
Katz et al[17] Bimatoprost 0.01% one drop in the affected eye(s) QD between 7 PM and 9 PM vs bimatoprost 0.0125% one drop in the affected eye(s) QD between 7 PM and 9 PM vs bimatoprost 0.03% one drop in the affected eye(s) QD between 7 PM and 9 PM	DB, MC, PRO, RCT Patients ≥18 years of age with a ocular hypertension, primary open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy or iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma in each eye and an 8 AM baseline IOP 22 to 34 mm Hg or less in each eye	N=561 12 months	Primary: Mean IOP and mean change from baseline IOP at each follow-up time point Secondary: Diurnal IOP and response rate (percentage of patients achieving a ≤20% decrease from baseline IOP	Primary: The mean IOPs during follow-up ranged from 16.4 to 17.9 mm Hg with bimatoprost 0.01%, 16.6 to 18.3 mm Hg with bimatoprost 0.0125% and 16.1 to 17.8 mm Hg with bimatoprost 0.03%. Bimatoprost 0.01%, but not bimatoprost 0.0125%, was NI in efficacy to bimatoprost 0.03% (upper limit of the 95% CI of the difference in mean IOP within 1.5 mm Hg at all time points and within 1 mm Hg at most time points). All bimatoprost strengths provided statistically significant reductions from baseline IOP at every evaluated time point. The mean reduction from baseline IOP ranged from 5.2 to 7.8 mm Hg with bimatoprost 0.01%, 5.2 to 7.5 mm Hg with bimatoprost 0.0125% and 5.6 to 8.0 mm Hg with bimatoprost 0.03%. After 12 months of treatment, the mean reduction from baseline IOP was 7.4 mm Hg (-29%) with bimatoprost 0.01%, 7.0 mm Hg (-28%) with bimatoprost 0.0125% and 7.6 mm Hg (-30%) with bimatoprost 0.03% at the 8 AM evaluation. At 12 noon, the average reduction in IOP from baseline was 5.8 mm Hg (-25%) with bimatoprost 0.01%, 5.6 mm Hg (-24%) with bimatoprost 0.0125% and 6.3 mm Hg (-27%) with bimatoprost 0.03%. At 4 PM, IOP was reduced from baseline by 5.2 mm Hg (-23%) with bimatoprost 0.01% and 0.0125% and by 5.6 mm Hg (-25%) with bimatoprost 0.03%. Secondary: The differences in diurnal IOP between bimatoprost 0.01% and bimatoprost 0.03% across all visits was 0.43 mm Hg, demonstrating NI (upper limit of the 95% CI of the difference in mean IOP within 0.93 mm Hg). The difference in IOP between bimatoprost 0.0125% and bimatoprost 0.03% was 0.56 mm Hg, establishing NI (upper limit of the 95% CI of the difference

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in mean IOP within 1.06 mm Hg). Bimatoprost 0.01% was equivalent to bimatoprost 0.03% in mean diurnal IOP during follow-up (limits of the 95% CI of the treatment difference within 1.5 mm Hg at all six follow-up visits and within 1.0 mm Hg at four visits). Bimatoprost 0.0125% was not equivalent to bimatoprost 0.03% in mean diurnal IOP (limits of the 95% CI of the treatment difference were within 1.5 mm Hg at all six follow-up visits but within 1.0 mm Hg at only one of the visits). At 12 months, a ≥20% decrease from baseline IOP was achieved at 8 AM by 79.6, 77.1 and 82.4% of patients treated with bimatoprost 0.01, 0.0125 and 0.03%, respectively. A ≥20% decrease from baseline IOP was achieved at 12 noon by 66.1, 63.8 and 73.8% of patients treated with bimatoprost 0.01, 0.0125 and 0.03%, respectively. A ≥20% decrease from baseline IOP was achieved at 4 PM by 58.1, 58.5 and 66.3% of patients treated with bimatoprost 0.01, 0.0125 and 0.03%, respectively.
Cheng et al[18] Bimatoprost 0.03% one drop in the affected eye(s) QPM vs latanoprost 0.005% one drop in the affected eye(s) QPM	MA of 13 RCTs Patients with glaucoma (>21 mm Hg and a glaucomatous visual field, optic disc changes, or retinal fiber layer defects) or ocular hypertension (IOP >21 mm Hg without medication and a normal visual field, optic disc, and	N=1,032 Up to 6 months	Primary: Percent reduction from baseline in IOP Secondary: Proportion of patients reaching target IOP ≤17 mm Hg	Primary: The WMD of the percent reduction in IOP was 2.59% (95% CI, 0.81 to 4.37; *P*=0.004), 2.41% (95% CI, 0.58 to 4.25; *P*=0.01) and 5.60% (95% CI, 2.95 to 8.26; *P*<0.001) favoring bimatoprost over latanoprost at one, three and six months, respectively. A post-hoc MA that excluded industry-sponsored trials found no significant difference between bimatoprost and latanoprost in the percent reduction in IOP from baseline in three trials reporting outcomes after one month (WMD, 2.21%; 95% CI, -3.25 to 7.67; *P* value not reported) and one trial reporting outcomes at three months (WMD, 1.13%; 95% CI, -7.38 to 9.64; *P* value not reported). In two trials, the WMD of the percent reduction in IOP at six months from baseline was 5.05% (95% CI, 0.26 to 9.83) favoring bimatoprost.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	retinal nerve fiber layer) and IOP between 22 and 38 mm Hg			Secondary: At three months, a significantly greater proportion of patients treated with bimatoprost reached the target IOP ≤17 mm Hg (50.0 vs 37.6%) compared to patients treated with latanoprost (pooled risk difference, 12%; 95% CI, 4 to 21; *P*=0.004). The differences in patients reaching target IOP at one (*P*=0.52) and six months (*P*=0.06) were not significant. Bimatoprost was associated with a significantly higher incidence of hyperemia compared to latanoprost (43.1 vs 22.6%; pooled risk difference, 20%; 95% CI, 15 to 24; *P*<0.001). The rates of ocular inflammation, cystoid macular edema, iris pigmentation, dry eye, eye irritation, eye pain, pruritus and visual disturbance were comparable between bimatoprost and latanoprost.
Cantor et al[19] Bimatoprost 0.03% one drop in the affected eye(s) QD between 7 PM and 9 PM vs travoprost 0.004% one drop in the affected eye(s) QD between 7 PM and 9 PM	AC, DB, MC, PG, PRO, RCT Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension or an untreated IOP ≥21 and ≤34 mm Hg	N=157 6 months	Primary: Mean change from baseline in IOP, proportion of patients reaching target IOP reduction Secondary: Physician's assessment of clinical success and adverse events	Primary: Mean reductions in IOP with bimatoprost at 9 AM, 1 PM and 4 PM were 7.1, 5.9 and 5.3 mm Hg, respectively. Mean reductions in IOP with travoprost at 9 AM, 1 PM and 4 PM were 5.7, 5.2, and 4.5 mm Hg, respectively. Differences between bimatoprost and travoprost in IOP changes were significant at 9 AM for all study visits (*P*<0.014) and at six months (*P*<0.001). The differences were not significant at the 1 PM (*P*=0.213) or 4 PM (*P*≥0.207) time points after six months. A ≥20.0% reduction in IOP occurred in 77.6% of bimatoprost-treated patients compared to 64.2% of travoprost-treated patients (*P*=0.065). A reduction in IOP ≥25.0% occurred in 64.5% of bimatoprost-treated patients compared to 39.5% of travoprost-treated patients (*P*=0.002). A reduction in IOP ≥30.0% occurred in 38.2% of bimatoprost-treated patients compared to 28.4% of travoprost–treated patients (*P*=0.194). Secondary: The rate of clinical success as determined by physician's assessment was higher in the bimatoprost group; however, this difference was not statistically significant (78.1 vs 68.0%; *P*=0.167).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Rates of ocular redness, ocular itching and hyperemia were comparable between the bimatoprost and travoprost groups.
Macky et al[20] Bimatoprost 0.03% one drop in the affected eye(s) QD between 9 PM and 10 PM vs travoprost 0.004% one drop in the affected eye(s) QD between 9 PM and 10 PM	AC, MC, PRO, RCT Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension and an IOP 21 to 35 mm Hg in each eye	N=72 6 months	Primary: Mean change from baseline in IOP at week two, month one, two, four and six Secondary: Adverse events and clinically successful treatment (continuing on treatment past six months based on efficacy and tolerability)	Primary: After six months of treatment, both bimatoprost and travoprost demonstrated statistically significant reductions from baseline IOP at all time points (*P*<0.001 for all). The largest reduction in IOP for each drug was achieved by week two of treatment. Bimatoprost provided greater mean IOP reductions from baseline compared to travoprost at each study visit, though these differences were not statistically significant. The mean reductions in IOP at week- two were 8.77 mm Hg (-33.39%) and 8.42 mm Hg (-31.54%) for bimatoprost and travoprost, respectively (*P*=0.703). By month six, bimatoprost lowered IOP further than travoprost (8.47 [-31.61%] vs 7.84 mm Hg [-29.50%]) although the difference was not statistically significant (*P*=0.536). Secondary: The most common adverse event in both treatment groups was ocular redness, occurring in seven bimatoprost patients and six patients treated with travoprost. The occurrence of ocular redness did not lead to discontinuation of treatment in either group. In the bimatoprost group, 85.3% of patients were considered to have successful treatment compared to 73.3% of travoprost-treated patients (*P*=0.456).
Kammer et al[21] Bimatoprost 0.03% one drop in the affected eye(s) QPM vs travoprost 0.004% one drop in the affected eye(s) QPM	AC, MC, PG, SB, RCT Adults with glaucoma or ocular hypertension in each eye with inadequate IOP control after ≥30 days on latanoprost monotherapy and	N=266 3 months	Primary: Mean IOP at each time point and mean diurnal IOP Secondary: Ocular signs on biomicroscopy, adverse events and visual acuity	Primary: After switching from latanoprost treatment, the mean IOP was significantly lower with bimatoprost compared to travoprost at 9 AM at month one (17.6 vs 18.3 mm Hg; *P*=0.004) but not at 4 PM (16.8 vs 17.0 mm Hg; *P*=0.162). By month three, IOP was similar between patients transitioned to bimatoprost or travoprost at 9 AM (17.6 vs 18.1 mm Hg; *P*=0.058); however, bimatoprost-treated patients had a significantly lower IOP at the 4 PM evaluation point compared to travoprost (16.5 vs 17.0 mm Hg; *P*=0.047). The mean diurnal IOP was significantly reduced when switching from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	best-corrected visual acuity equivalent to a Snellen score of 20/100 or better in each eye			latanoprost to bimatoprost compared to travoprost at months one (1.9 vs 1.2; *P*=0.009) and three (2.1 vs 1.4 mm Hg; *P*=0.024). Secondary: On biomicroscopy, conjunctival hyperemia and punctate keratitis were the only findings with one-grade or more increases in severity reported in at least 4% of patients in either treatment group. At three months, the proportions of patients with a one-grade, two-grade or three-grade increase in the severity of conjunctival hyperemia, respectively, were 8.4, 2.3 and 0.8% in the bimatoprost group and 13.5, 3.0 and 0.0% in the travoprost group. No patients discontinued treatment due to conjunctival hyperemia or punctuate keratitis. Adverse events were reported in 11 patients (8.4%) in the bimatoprost group and eight patients (6.0%) in the travoprost group (*P*=0.485). Ocular or conjunctival hyperemia was reported as a treatment-related adverse event for 3.1% of bimatoprost patients and 1.5% of travoprost patients (*P*=0.445). There was no significant between-group difference in the change from baseline visual acuity.
Chander et al[22] Bimatoprost 0.03% one drop in the affected eye(s) QD at 9 PM vs travoprost 0.004% one drop in the affected eye(s) QD at 9 PM	AC, PRO, RCT Patients ≥18 years of age with primary open-angle glaucoma and an IOP 21 to 34 mm Hg in each eye	N=31 12 weeks	Primary: Mean change in IOP from baseline and percentage reduction of IOP at 9 AM, 1 PM and 4 PM at 12 weeks Secondary: Adverse events	Primary: The mean reduction from baseline in IOP at 12 weeks in the bimatoprost group was 36.28% at 9.00 AM, 34.5% at 1 PM and 34.8% at 4 PM. In the travoprost group, the reduction in IOP was 31.6% at 9 AM, 28.7% at 1 PM and 27.08% 4 PM respectively. The improvement from baseline in IOP at 9 AM was significant for both treatment groups; however, significantly greater reductions were achieved with bimatoprost (*P*<0.001). Patients treated with bimatoprost experienced greater reductions in IOP at 9 AM at all points compared to the travoprost group; however, the difference was only significant at 12 weeks (*P*=0.024). Both treatment groups experienced significant reductions from baseline in IOP at 1 PM (*P*<0.001 for all points). Although the mean IOP reductions in the bimatoprost group were greater compared to the travoprost at every 1 PM study visit, there was no significant difference at 12 weeks (*P*=0.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatment groups experienced significant reductions from baseline in IOP at 4 PM at all study visits (*P*<0.001 for all). The reductions in IOP were significantly greater in the bimatoprost group compared to the travoprost group at every study visit (*P*=0.03). At 12 weeks, the overall decrease in IOP in the bimatoprost group was significantly greater than the IOP reduction observed in the travoprost group (34.94 vs 28.02%; *P*=0.03). Secondary: The most commonly reported adverse event was ocular redness in both treatment groups. In the bimatoprost group, 12.5% patients complained of mild ocular redness compared to 13.3% of patients in the travoprost group. Overall, 12.5% of patients in the bimatoprost group experienced ocular itching while there were no complaints of ocular itching in the travoprost group. There was an increase in eye lashed in 6.3% of patients treated with bimatoprost compared to zero patients in the travoprost group. No significant differences in adverse events were reported between treatment groups.
Sawada et al[23] Latanoprost 0.005% one drop in the affected eye(s) QD at 9 PM vs travoprost 0.004% one drop in the affected eye(s) QD at 9 PM	AC, OL, PRO, RCT, XO Patients with open-angle glaucoma	N=42 XO at 12 weeks, 24 weeks total	Primary: Change from baseline in IOP, CCT and adverse events Secondary: Not reported	Primary: There was a significant reduction from baseline in diurnal IOP with latanoprost and travoprost (*P*<0.001). The differences in the IOPs for the individual times points were not significant between the two treatments (*P*=1.000 for all time points). The mean diurnal IOP was 11.4 mm Hg in both the latanoprost and travoprost groups (*P*=0.9158), and the mean percent reduction from the baseline for patients with latanoprost was 17.3 and 16.9% with travoprost (*P*=0.60). The CCT decreased significantly from baseline in patients initially receiving travoprost, to 528.3 µm at month three, 530.2 µm at month four and 528.42 µm at six months (*P*=0.0041, 0.0048 and 0.0011 respectively). There was a significant reduction in CCT at six months in eyes initially treated with latanoprost compared to baseline (*P*=0.0473).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Mild bulbar conjunctival hyperemia was the most frequently reported adverse event, (11 latanoprost patients and 20 travoprost patients; P=0.07). Hypertrichosis was observed in one patient treated with travoprost.

Secondary:
Not reported</td></tr>
<tr><td>Enoki et al[24]

Latanoprost 0.005% one drop in the affected eye(s) QD

vs

unoprostone* 0.12% one drop in the affected eye(s) BID</td><td>OL, OS, PRO

Patients previously treated with unoprostone for ≥3 months to treat normal-tension, open-angle glaucoma, with glaucomatous changes and defects</td><td>N=34

3 months</td><td>Primary:
Changes in IOP at one, two and three months

Secondary:
Changes in IOP in patients with an IOP >12 mm Hg and ≤12 mm Hg and adverse events</td><td>Primary:
Treatment with latanoprost significantly reduced IOP compared to treatment with unoprostone at one, two and three months, respectively (1.8, 2.9 and 2.3 mm Hg; P<0.001 for all).

Secondary:
Patients with an IOP >12 mm Hg during unoprostone treatment experienced significant reductions in IOP of following treatment with latanoprost for one, two and three months, respectively (2.1, 3.2 and 2.9 mm Hg ; P<0.0001).

Patients with an IOP ≤12 mm Hg during unoprostone treatment had significant reductions in IOP at month two (1.9 mm Hg; P<0.0001), but changes were comparable at months one and three (P values not reported).

One patient reported ocular foreign sensation with latanoprost. No serious adverse events were observed.</td></tr>
<tr><td>Jampel et al[25]

Latanoprost 0.005% one drop in the affected eye(s) QPM

vs

unoprostone* 0.12% one drop in the affected eye(s) BID</td><td>DB, MC, PG, PRO, RCT

Patients ≥18 years of age, current or previous treatment for IOP control</td><td>N=165

8 weeks</td><td>Primary:
Change in IOP at 8 AM, 12 noon and 4 PM by week eight

Secondary:
Mean percent change from baseline in IOP, proportion of patients achieving specific IOP</td><td>Primary:
Changes in IOP at all individual time points were significantly greater with latanoprost compared to unoprostone (P<0.001).

<table>
<tr><td colspan="5">IOPs Across Treatment Groups (mean±SD)</td></tr>
<tr><td></td><td>8 AM</td><td>12 noon</td><td>4 PM</td><td>Pooled Mean</td></tr>
<tr><td>Latanoprost (baseline)</td><td>27.1±2.3</td><td>25.1±3.6</td><td>23.9±3.7</td><td>25.3±2.8</td></tr>
<tr><td>Latanoprost (eight weeks)</td><td>18.8±3.0</td><td>18.2±3.0</td><td>17.6±3.3</td><td>18.2±2.8</td></tr>
<tr><td>Latanoprost reduction</td><td>8.3±3.1</td><td>6.9±3.9</td><td>6.3±4.0</td><td>7.2±3.2</td></tr>
<tr><td>Unoprostone (baseline)</td><td>27.3±3.1</td><td>24.8±3.3</td><td>24.3±3.5</td><td>25.5±3.3</td></tr>
<tr><td>Unoprostone (eight weeks)</td><td>21.6±4.0</td><td>21.5±4.2</td><td>20.6±3.9</td><td>21.6±4.0</td></tr>
<tr><td>Unoprostone reduction</td><td>5.2±3.5</td><td>3.2±2.7</td><td>3.5±3.7</td><td>3.9±2.6</td></tr>
</table></td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			levels and adverse events	<table><tr><td>Latanoprost vs unoprostone</td><td>(*P*<0.001)</td><td>(*P*<0.001)</td><td>(*P*<0.001)</td><td>(*P*<0.001)</td></tr></table> Secondary: The mean percent reduction in IOP was significantly greater with latanoprost compared to unoprostone (28 vs 15%; *P*<0.001). IOP reductions >40 and >30% occurred in 15 and 45% of patients treated with latanoprost, respectively. In comparison, this was seen in zero and 6% of patients treated with unoprostone, respectively. Eye irritation and eye pain were reported in 42 and 23% of unoprostone and latanoprost patients, respectively. No changes in iris pigmentation were observed in either group.
Parrish et al[26] Bimatoprost 0.03% one drop in the affected eye(s) QD at 8 PM vs latanoprost 0.005% one drop in the affected eye(s) QD at 8 PM vs travoprost 0.004% one drop in the affected eye(s) QD at 8 PM	AC, DB, MC, PG, RCT Patients ≥18 years of age with primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular hypertension (≥21 mm Hg) and current or previous therapy with topical ocular hypotensive agent	N=410 12 weeks	Primary: Mean change in IOP at 8 AM at 12 weeks Secondary: Mean change in diurnal IOP and adverse events	Primary: At week 12, the mean reductions in IOP were 8.7±0.3, 8.6±0.3, 8.0±0.3 mm Hg in the bimatoprost, latanoprost and travoprost groups, respectively. All of these changes were significant compared to baseline (*P*<0.001). The reductions were similar among treatment groups (*P*=0.128). Secondary: Mean changes in diurnal IOP were similar across all treatment groups and at all time points. At least one adverse event was reported by 75.9, 64.0 and 68.8% of patients in the bimatoprost, latanoprost and travoprost groups, respectively. Significantly fewer patients in the latanoprost group reported an ocular adverse event compared to those receiving either bimatoprost or travoprost (*P*=0.003). The most frequently reported adverse event, hyperemia, was reported by 68.6, 47.1 and 58.0% of patients in the bimatoprost, latanoprost and travoprost groups, respectively. Hyperemia occurred significantly more frequently in the bimatoprost group compared to the latanoprost group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Faridi et al[27] Bimatoprost 0.03% one drop in the affected eye(s) QPM vs latanoprost 0.005% one drop in the affected eye(s) QPM vs travoprost 0.004% one drop in the affected eye(s) QPM	AC, PRO, RCT, SB Newly diagnosed patients with ocular hypertension or open-angle glaucoma, including normal tension glaucoma	N=122 6 months	Primary: Change from baseline in IOP after two and six months and tolerance profiles Secondary: Not reported	Primary: After two months of treatment, patients receiving bimatoprost experienced a significantly greater reduction in IOP compared to patients receiving latanoprost and travoprost (9.45 vs 6.17 and 7.36 mm Hg, respectively; *P*=0.013). At six months, bimatoprost treatment reduced IOP from baseline compared to latanoprost and travoprost; however, the difference was not statistically significant (9.23 vs 7.57 and 7.81 mm Hg, respectively; *P*=0.15). No difference in tolerance was observed between bimatoprost, latanoprost and travoprost at two months (*P*=0.11) and six months (*P*=0.86). Adverse event profiles were similar between the groups (*P*=0.60 and *P*=0.34) at the two-month and six-month follow-up visits, respectively. Secondary: Not reported
Aptel et al[28] Bimatoprost 0.03% one drop in the affected eye(s) QPM between 6 PM and 10 PM vs latanoprost 0.005% one drop in the affected eye(s) QPM between 6 PM and 10 PM vs travoprost 0.004% one drop in the affected eye(s) QPM between 6 PM and 10 PM	MA of 8 RCTs Patients with open-angle glaucoma or ocular hypertension receiving prostaglandin analogue monotherapy	N=1,610 3 months	Primary: Mean change from baseline in IOP at 8 AM, 12 noon, 4 PM and 8 PM Secondary: Conjunctival hyperemia	Primary: The difference in absolute IOP reduction from baseline was significantly greater with bimatoprost at all time points compared to latanoprost (8 AM: WMD, 0.50 mm Hg; 95% CI, 0.01 to 0.99; *P*=0.05; 12 noon: WMD, 1.17 mm Hg; 95% CI, 0.68 to 1.66; *P*<0.001; 4 PM: WMD, 0.78 mm Hg; 95% CI, 0.26 to 1.29; *P*=0.003; 8 PM: WMD, 0.67 mm Hg; 95% CI, 0.02 to 1.32; *P*=0.04). The difference in absolute IOP reduction from baseline was significantly greater with bimatoprost at 8 AM (WMD, 1.02 mm Hg; 95% CI, 0.32 to 1.72; *P*=0.004) and 12 noon (WMD, 0.86 mm Hg; 95% CI, 0.12 to 1.59; *P*=0.02) compared to travoprost. No statistically significant difference occurred between bimatoprost and travoprost at 4 PM (*P*=0.190) or 8 PM (*P*=0.070). Reductions in IOP were comparable between latanoprost and travoprost at 8 AM (*P*=0.100), 12 noon (*P*=0.380), 4 PM (*P*=0.820) and 8 PM (*P*=0.670). Secondary: The incidence of hyperemia was significantly higher with bimatoprost compared to latanoprost (0.48 vs 0.26%; RR, 1.70; 95% CI, 1.44 to 2.02;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.001) and travoprost (0.51 vs 0.42%; RR, 1.19; 95% CI, 1.00 to 1.42; *P*=0.05). The incidence of self-reported hyperemia was significantly higher with travoprost compared to latanoprost (0.53 vs 0.36%; RR, 1.45; 95% CI, 1.22 to 1.72; *P*<0.001).
Denis et al[29] Bimatoprost 0.03% one drop in the affected eye(s) QPM vs latanoprost 0.005% one drop in the affected eye(s) QPM vs travoprost 0.004% one drop in the affected eye(s) QPM	MA of 9 RCTs Patients with open-angle glaucoma or ocular hypertension	N=1,318 Duration varied from 2 weeks to 12 months; mean time of follow up was 4.3 months	Primary: Average IOP at the end of follow up period Secondary: Adjusted treatment effect on IOP at the end of follow up period, adjusting for baseline and duration of follow-up	Primary: The order of average IOP at the end of the follow-up period was bimatoprost (16.47 mm Hg; 95% CI, 15.68 to 17.26), travoprost (16.89 mm Hg; 95% CI, 15.69 to 18.10) and latanoprost (17.42 mm Hg; 95% CI, 16.48 to 18.36). Secondary: Using latanoprost as the reference product, patients treated with bimatoprost and travoprost showed similar reductions in adjusted IOP levels at follow up. Patients treated with bimatoprost had an absolute difference in IOP of -1.04 mm Hg compared to latanoprost (95% CI, -2.11 to 0.04). Patients treated with travoprost had an absolute difference in IOP of -0.98 mm Hg compared to latanoprost (95% CI, -2.08 to 0.13).
Crichton et al[30] Dorzolamide/timolol (Cosopt®) 1 drop in each eye twice daily for 6 weeks, if IOP goal was not reached at that time, latanoprost (Xalatan®) was added for another 6 weeks	MC, OL, PRO Patients 18 years of age or older, newly diagnosed with open-angle glaucoma or ocular hypertension, with an IOP of at least 27 mm Hg in at least one eye	N=164 12 weeks	Primary: Absolute and percent change in IOP from baseline to six and 12 weeks of treatment Secondary: Proportion of patients achieving target IOP, proportion of patients	Primary: At week-six, the mean absolute and percent IOP reduction for the total population was 11.1 and 13.9%, respectively. Between weeks six and 12, the mean absolute and percent changes in IOP were not significant among patients treated with dorzolamide/timolol. However, patients who had received the additional latanoprost experienced a statistically significant improvement in IOP (mean and percent reductions) between six and 12 weeks of therapy (*P*<0.05). Secondary: IOP reduction of at least 5 mm Hg was achieved by 92.1% of patients at week-six of therapy (*P*<0.001).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td>achieving therapeutic response (reduction of 5 mm Hg or 20% in IOP from baseline) at six and 12 weeks, safety</td><td>At week-12, an IOP reduction of at least 5 mm Hg or 20% was noted in 97% of patients in the dorzolamide/timolol group and in 87.5% of patients in the dorzolamide/timolol and latanoprost group.

Therapeutic target was achieved by 86.6% of patients who had received dorzolamide/timolol after six weeks of therapy. In contrast, therapeutic target was achieved by 58.3% of patients after 12 weeks of therapy (P=0.002).

Between weeks six and 12, dorzolamide/timolol combination therapy was effective in sustaining therapeutic response. The addition of latanoprost reduced the IOP by an additional 6.3 mm Hg (20.1%).

At week-12, dorzolamide/timolol recipients experienced a reduction in IOP from baseline of 12.2 mm Hg or 11.9% (P<0.001). Patients who had received dorzolamide/timolol in combination with latanoprost experienced IOP reduction of 13.4 mm Hg or 15.7% (P<0.001).

Treatment-related adverse events were reported by 14 and 21.4% of patients receiving dorzolamide/timolol and dorzolamide/timolol and latanoprost combination therapy, respectively. Eye disorders and nervous system disorders were the most frequently reported adverse events.</td></tr>
<tr><td>Sharpe et al[31]

Bimatoprost 0.03% 1 drop in the affected eye(s) QPM

vs

dorzolamide/timolol 2%/0.5% 1 drop in the affected eye(s) BID</td><td>AC, DB, PRO, RCT, XO

Patients ≥18 years of age, bilateral open-angle glaucoma, IOP between 22 and 29 mm Hg, visual acuity of 20/200 or better, no laser or eye surgery 30 days prior to study initiation, and an insufficient</td><td>N=30

6 weeks of treatment, followed by 6 week XO</td><td>Primary:
Diurnal IOP (average of seven measurements) at week six of therapy

Secondary:
IOP at individual time points, mean diurnal range, mean peak IOP, reduction of IOP</td><td>Primary:
Bimatoprost showed statistically significant differences in mean diurnal IOP reductions from baseline compared to dorzolamide/timolol (18.8±2.5 vs 17.6±2.0 mm Hg; P=0.03).

<table><tr><td colspan="5">Absolute IOPs (mm Hg±SD)</td></tr><tr><td>Time</td><td>Baseline</td><td>Dorzolamide/timolol</td><td>Bimatoprost</td><td>P value</td></tr><tr><td>8 AM</td><td>25.1±2.0</td><td>19.7±3.1</td><td>18.5±2.4</td><td>0.02</td></tr><tr><td>10 AM</td><td>24.3±2.4</td><td>18.4±3.1</td><td>17.4±2.4</td><td>0.04</td></tr><tr><td>12 PM</td><td>24.1±2.7</td><td>18.2±3.2</td><td>17.1±2.3</td><td>0.10</td></tr><tr><td>2 PM</td><td>24.2±2.9</td><td>18.4±2.7</td><td>17.3±2.3</td><td>0.06</td></tr><tr><td>4 PM</td><td>24.5±3.2</td><td>18.7±2.4</td><td>17.8±2.4</td><td>0.02</td></tr><tr><td>6 PM</td><td>24.8±3.2</td><td>18.9±2.6</td><td>18.1±2.3</td><td>0.05</td></tr><tr><td>8 PM</td><td>25.1±3.3</td><td>19.2±2.6</td><td>18.4±.4.0</td><td>0.18</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td>response to latanoprost (IOP ≥21 mm Hg)</td><td></td><td>from baseline, visual acuity, adverse events</td><td>
<table>
<tr><td>Mean diurnal curve</td><td>24.6±2.6</td><td>18.8±2.5</td><td>17.6±2.0</td><td>0.03</td></tr>
<tr><td>Range</td><td>-</td><td>4.0±1.8</td><td>3.2±1.3</td><td>0.2</td></tr>
<tr><td>Peak</td><td>-</td><td>20.8±2.5</td><td>19.4±2.2</td><td>0.03</td></tr>
</table>

Secondary:
Bimatoprost compared to dorzolamide/timolol showed a statistically significant reduction in diurnal range (4.0±1.8 vs 3.2±1.3 mm Hg; P=0.02) and peak IOP (20.8±2.5 vs 19.4±2.2 mm Hg; P=0.003).

Significantly more stinging was reported with dorzolamide/timolol (P<0.0001). Overall there were 17 ocular adverse events with dorzolamide/timolol compared to five with bimatoprost.</td></tr>
<tr><td>Ozturk et al[32]

Dorzolamide/timolol 2%/0.5% one drop in the affected eye(s) BID

vs

bimatoprost 0.03% one drop in the affected eye(s) QD</td><td>OL, PRO, RCT, SB

Patients with open, normal-appearing angles and either primary open angle glaucoma or ocular hypertension with an IOP >21 mm Hg at the baseline visit</td><td>N=65

6 months</td><td>Primary:
Reduction in IOP

Secondary:
Adverse events</td><td>Primary:
Differences in IOP between the two treatment groups were not found to be statistically significant at all study visits (P>0.05 for all). The mean reduction in IOP was 6.5±2.3 mm Hg in the dorzolamide/timolol group and 6.2±1.8 mm Hg in the bimatoprost group (P=0.48).

Secondary:
No statistically significant differences were found with regards to the occurrence of burning and/or stinging, bitter taste, dry eye, eyelid eczema, or breathlessness (P=0.31, P=0.47, P=0.55, P=0.47, and P=0.47 respectively).

Conjunctival hyperemia did occur in significantly more patients in the dorzolamide/timolol group than in the bimatoprost group (P=0.02).</td></tr>
<tr><td>Li et al[33]

Bimatoprost 0.03%

vs

latanoprost 0.005%</td><td>MA of 12 RCT’s

Patients with open-angle glaucoma or ocular hypertension</td><td>N=3,048

Duration varied from 2 weeks to 12 months</td><td>Primary:
Mean IOP over treatment visits

Secondary:
Incidence of reported side effects</td><td>Primary:
Travoprost 0.004% was more effective than timolol in lowering IOP (WMD, -0.81 mm Hg; 95% CI, -1.16 to 0.45; P=0.00001).

The WMD in IOP between travoprost 0.004% and bimatoprost was not statistically significant (0.08 mm Hg; 95% CI, -0.62 to 0.79; P=0.8).

The WMD in IOP between travoprost 0.004% and latanoprost was also not</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs travoprost 0.004% vs travoprost 0.0015%† vs unoprostone 0.12%* vs timolol 0.05% Dosing not specified for any of the regimens.				statistically significant (-0.57 mm Hg; 95% CI, -1.18 to 0.04; *P*=0.07). Treatment with travoprost 0.004% resulted in significantly lower IOP than travoprost 0.0015% (-0.32 mm Hg; 95% CI, -0.62 to -0.02; *P*=0.04). One trial showed that travoprost 0.004% was more effective than unoprostone in lowering IOP (*P* value not reported). Secondary: Travoprost 0.004% had a higher incidence of ocular hyperemia than timolol (OR, 6.76; 95% CI, 4.93 to 9.25; *P*<0.00001) and latanoprost (OR, 2.03; 95% CI, 1.49 to 2.75; *P*<0.00001). The difference in rates of hyperemia between travoprost 0.004% and bimatoprost did not reach statistical significance (OR, 0.65; 95% CI, 0.42 to 1.00; *P*=0.05). Travoprost 0.004% caused a higher percentage of eyelash changes than timolol (OR, 11.06; 95% CI, 2.07 to 59.08; *P*=0.005), latanoprost (OR, 3.82; 95% CI, 2.50 to 5.84; *P*<0.00001) and travoprost 0.0015% (OR, 1.79; 95% CI, 1.40 to 2.27; *P*<0.00001). There were no statistically significant differences in eyelash changes between travoprost 0.004% and bimatoprost.
Cheng et al[34] Bimatoprost 0.03% 1 drop in the affected eye(s) QPM vs latanoprost 0.005% 1 drop in the affected eye(s) QPM vs betaxolol 0.25 or 0.5% 1 drop in the affected eye(s) BID	MA of 15 RCT's Patients with a diagnosis of normal tension glaucoma as defined by: a untreated peak IOP reading within normal range; the open, normal-appearing anterior chamber angle; the presence of typical glaucomatous visual field defects and corresponding	N=450 Duration varied from 3 to 8 weeks	Primary: Absolute and relative reductions in IOP from baseline for peak and trough Secondary: Not reported	Primary: The highest reduction in IOP at peak was seen in patients treated with brimonidine (relative reduction, 24%; 95% CI, 13 to 31; absolute reduction, 3.6 mm Hg; 95% CI, 2.4 to 4.9); followed by bimatoprost (21; 95% CI, 16 to 25; 3.4; 95% CI, 2.7 to 4.2), latanoprost (20; 95% CI, 17 to 24; 3.3; 95% CI, 2.7 to 3.8), timolol (15; 95% CI, 12 to 18; 2.4; 95% CI, 2.0 to 2.8), dorzolamide (14; 95% CI, 8 to 19; 2.1; 95% CI, 1.3 to 3.0), brinzolamide (13.0; 95% CI, 6.0 to 20.0; 1.9; 95% CI, 0.9 to 2.9), and betaxolol (12; 95% CI, 1.0 to 23.0; 2.0; 95% CI, 0.2 to 3.7). The highest reduction in IOP at trough was seen in patients treated with latanoprost (relative reduction, 20.0%; 95% CI, 18.0 to 23.0; absolute reduction, 3.3 mm Hg; 95% CI, 2.9 to 3.6); followed by bimatoprost (18.0; 95% CI, 14.0 to 22.0; 2.9; 95% CI, 2.2 to 3.5), timolol (18.0; 95% CI, 8.0 to 27.0; 3.0; 95% CI, 1.7 to 4.3), dorzolamide (12.0; 95% CI, -7.0 to 31.0; 3.0; 95% CI, 1.7 to 4.3), and brimonidine (11.0; 95% CI, 7.0 to 14.0; 1.7; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs brimonidine 0.2% 1 drop in the affected eye(s) BID vs brinzolamide 1.0% 1 drop in the affected eye(s) TID vs dorzolamide 2.0% 1 drop in the affected eye(s) TID vs timolol 0.5% 1 drop in the affected eye(s) BID	optic disc damage; and the absence of a secondary cause for IOP elevation			1.1 to 2.3). Study results suggest that latanoprost, bimatoprost, and timolol are the most effective agents for lowering IOP in patients with normal tension glaucoma. Secondary: Not reported
van der Valk R et al[16] Bimatoprost 0.03% 1 drop in the affected eye(s) QD vs latanoprost 0.005% 1 drop in the affected eye(s) QD vs travoprost 0.004% 1 drop in the affected eye(s) QD vs	MA of 28 RCT's Over 85% of patients diagnosed with open- angle glaucoma or ocular hypertension	N=6,953,6841 (for intraocular changes at trough, peak respectively) 1 month	Primary: Relative change in peak and trough IOP from baseline at one month Secondary: Not reported	Primary: The order of highest mean reduction of IOP seen at peak from baseline among intraocular lowering agents was bimatoprost (33%; 95% CI, 31 to 35), latanoprost (31%; 95% CI, 29 to 33), travoprost (31%; 95% CI, 29 to 32), timolol (27%; 95% CI, 25 to 29), betaxolol (23%; 95% CI, 22 to 25), brimonidine (25%; 95% CI, 22 to 28), brinzolamide (17%; 95% CI, 15 to 19), dorzolamide (22%; 95% CI, 20 to 24), and placebo (5%; 95% CI, 1 to 9). The order of highest mean reduction of IOP seen at trough from baseline was travoprost (29%; 95% CI, 25 to 32), bimatoprost (28%; 95% CI, 27 to 29) latanoprost (28%; 95% CI, 26 to 30), timolol (26%; 95% CI, 25 to 28), betaxolol (20%; 95% CI, 17 to 23), brimonidine (18%; 95% CI, 14 to 21), brinzolamide (17%; 95% CI, 15 to 19), dorzolamide (17%; 95% CI, 15 to 19), and placebo (5%; 95% CI, 0 to 10). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
betaxolol 0.5% 1 drop in the affected eye(s) BID vs brimonidine 0.2% 1 drop in the affected eye(s) BID vs brinzolamide 1% 1 drop in the affected eye(s) TID vs dorzolamide 2% 1 drop in the affected eye(s) BID to TID vs timolol 0.5% 1 drop in the affected eye(s) BID vs placebo				
Varma et al[35] Latanoprost 0.005% 1 drop in the affected eye(s) QPM vs timolol 0.5% 1 drop in the affected eye(s) BID	MA of 3 RCT's Patients with open-angle glaucoma or ocular hypertension	N=631 26 weeks	Primary: Post-treatment IOP range Secondary: Not reported	Primary: The changes in IOP range (mean±SD) between latanoprost and timolol compared to baseline were similar (-1.23±3.12 vs -0.92±2.83 mm Hg; *P*=0.196). High inter-visit IOP range (>6 mm Hg) was more frequently seen in timolol patients compared to latanoprost patients (6 vs 11%; *P*=0.026). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Zhang et al[36] Latanoprost 0.005% or 0.006%† 1 drop in the affected eye(s) QD vs timolol 0.5% 1 drop in the affected eye(s) BID	MA of 11 RCT's Patients with open-angle glaucoma or ocular hypertension	N=1,256 Duration varied from 1 to 12 months	Primary: Percentage IOP reduction; RR, risk difference, and number needed to harm for hyperemia, conjunctivitis, increased pigmentation, hypotension, and bradycardia; reduction in systemic blood pressure and heart rate Secondary: Not reported	Primary: Both drugs significantly lowered IOP. Latanoprost showed better IOP lowering effects than timolol with an additional 4 to 7% reduction, or 1.6 mm Hg (P<0.001). The difference was statistically significant in all trials except for the result from a single 12 month study, which was the longest included. Latanoprost caused hyperemia in more patients than timolol. The risk for hyperemia was over twice that seen with timolol (RR, 2.20; 95% CI, 1.33 to 3.65). The number needed to harm was 21 relative to timolol. Latanoprost caused iris pigmentation in 21 of 478 (4.39%) patients, compared to 0 of 387 patients treated with timolol (RR, 8.01; 95% CI, 1.87 to 34.30). Patients treated with timolol had a significant reduction in heart rate of four beats/minute (95% CI, 2 to 6). Secondary: Not reported
Lesk et al[37] Dorzolamide/timolol 2.0%/0.5% one drop into affected eye(s) BID and latanoprost 0.005% one drop into affected eye(s) QD vs dorzolamide/timolol 2.0%/0.5% one drop into affected eye(s) BID	MC, OL, PRO Patients 18 years of age and older, with a diagnosis of primary open angle glaucoma or ocular hypertension, who were previously treated with latanoprost monotherapy for four or more weeks but continued to have an IOP >21 mm Hg,	N=350 12 weeks	Primary: Reduction in IOP from baseline Secondary: Therapeutic response defined as a decrease >20% in IOP from baseline and adverse events	Primary: Both groups reported statistically significant changes in mean absolute and percent reductions in IOP at six and twelve weeks when compared to baseline (P<0.001). The changes in IOP between the groups at weeks six and twelve were not found to be statistically significant (P value not reported). Secondary: Therapeutic response rates >20% occurred after twelve weeks of treatment in 66.4% of the patients in the dorzolamide/timolol with latanoprost group and 52.9% of the patients in the dorzolamide/timolol group (P value not reported). The most frequent adverse events reported for both groups were eye irritation and bad taste in the mouth (12.0 and 4.3%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	deterioration of the visual fields regardless of IOP target, target IOP not achieved with latanoprost monotherapy, or an insufficient response in IOP reduction (<15% reduction) with latanoprost			
Fechtner et al[38] Dorzolamide/timolol 2%/0.5% 1 drop into both eye(s) BID vs latanoprost 0.005% 1 drop into both eyes QD	2 DB, MC, PG, RCT Patients ≥18 years of age diagnosed with bilateral open angle glaucoma or ocular hypertension	Study 1 N=256 Study 2 N=288 3 months	Primary: Mean change from baseline in daytime diurnal IOP Secondary: Assessment of safety and tolerability	Primary: Study 1: Both treatment groups reduced IOP between 25 to 30%. When the groups were compared at three months, the mean reduction in IOP was -0.44 mm Hg greater with dorzolamide/timolol than latanoprost (CI, -0.85 to 0.77). Study 2: Both treatment groups reduced IOP between 25 to 30%. When the groups were compared at three months, the mean reduction in IOP was -0.57 mm Hg greater with dorzolamide/timolol than latanoprost (CI, -1.31 to 0.16). Secondary: Study 1: Adverse events that occurred with both groups were mild to moderate and localized to the eye. The most common adverse events seen with both medications were ocular stinging, ocular itching, blurred vision, conjunctival hyperemia and taste perversion. The two most common adverse events in the study were ocular stinging (23 vs 7%) and taste perversion (10 vs 2%) which occurred significantly more in the dorzolamide/timolol group vs the latanoprost group (P<0.05). Study 2: Adverse events that occurred with both groups were mild to moderate and localized to the eye. The most common adverse events seen with both

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>medications were ocular stinging, ocular itching, blurred vision, conjunctival hyperemia and taste perversion.

The most common adverse event in the study was ocular stinging (10 vs 2%) which occurred significantly more in the dorzolamide/timolol group vs the latanoprost group (P<0.05).

Taste perversion occurred in only 2% of the time in the dorzolamide/timolol group and was not present in the latanoprost group; however, the results were not significant (P value not reported).</td></tr>
<tr><td>Konstas et al[39]

Dorzolamide/timolol 2%/0.5% 1 drop into affected eye(s) BID

vs

latanoprost 0.005%1 drop into affected eye(s) QD

After six months, the patients were XO to receive the alternative treatment.</td><td>PRO, RCT, SB, XO

Patient 39 years of age or older with a diagnosis of primary open angle glaucoma or ocular hypertension who were adequately controlled on either dorzolamide/timolol or latanoprost for >6 months and demonstrated an IOP ≥24 mm Hg after six weeks without treatment</td><td>N=58

12 months</td><td>Primary:
24 hour assessment of IOP, measured at 10 AM, 2 PM, 6 PM, 10 PM, 2 AM)

Secondary:
Assessment of safety and tolerability</td><td>Primary:
Both latanoprost and dorzolamide/timolol significantly reduced baseline 24 hour IOP (P=0.03). When the groups were directly compared, the difference in the change in IOP was not significant.

<table>
<tr><th>Time Points</th><th>Baseline</th><th>Latanoprost</th><th>Dorzolamide/Timolol</th><th>P value</th></tr>
<tr><td>6 AM</td><td>26.1±3.4</td><td>18.4±2.4</td><td>18.8±2.3</td><td>-</td></tr>
<tr><td>10 AM</td><td>27.9±2.9</td><td>18.6±2.5</td><td>17.8±2.0</td><td>-</td></tr>
<tr><td>2 PM</td><td>25.6±3.4</td><td>18.1±2.2</td><td>17.9±2.4</td><td>-</td></tr>
<tr><td>6 PM</td><td>24.9±2.3</td><td>18.2±2.2</td><td>18.4±2.5</td><td>-</td></tr>
<tr><td>10 PM</td><td>24.3±2.6</td><td>18.5±2.0</td><td>17.4±2.5</td><td>-</td></tr>
<tr><td>2 AM</td><td>23.3±2.5</td><td>17.6±2.5</td><td>18.0±2.3</td><td>-</td></tr>
<tr><td>24 hour</td><td>25.2±2.3</td><td>18.3±1.9</td><td>18.1±1.9</td><td>0.3</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td>Maximum</td><td>28.2±3.1</td><td>20.0±2.2</td><td>20.1±2.3</td><td>0.8</td></tr>
<tr><td>Minimum</td><td>22.5±2.0</td><td>16.5±2.1</td><td>16.4±2.0</td><td>0.5</td></tr>
<tr><td>Range</td><td>5.7±2.2</td><td>3.5±1.5</td><td>3.7±1.7</td><td>0.4</td></tr>
</table>

Secondary:
Adverse events reported in both groups were mild to moderate. Significantly more patients reported hypertrichosis (7 vs 0; P=0.02), headaches (6 vs 0; P=0.04), and ocular itching (12 vs 1; P=0.004) in the latanoprost group, while more patients in the dorzolamide/timolol group reported burning and stinging (30 vs 6; P<0.0001), and bitter taste (16 vs 0; P=0.0002).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Other adverse events that were reported by patients in the latanoprost and the dorzolamide/timolol group were conjunctival hyperemia (9 vs 4; *P*=0.1), superficial punctuate keratitis (6 vs 7; *P*=1.0), dry eye sensation (3 vs 7; *P*=0.3), foreign body sensation (4 vs 3; *P*=1.0), hyperchromia of iris (5 vs 0; *P*=0.07), and watering (3 vs 1; *P*=0.6).
Cheng et al[40] Latanoprost 0.005% 1 drop in the affected eye(s) QD vs dorzolamide 1 to 2% 1 drop in the affected eye(s) BID to TID combined with timolol 0.5% 1 drop in the affected eye(s) BID (includes both concomitant and fixed-combination administration)	MA of 14 RCT's Patients with glaucoma (excluding normal tension glaucoma) or ocular hypertension	N=2,149 Duration varied from 4 weeks to 6 months	Primary: Reduction from baseline to endpoint in diurnal mean IOP Secondary: Reduction from baseline to endpoint in IOP at 10 AM within a range of ±1 hour	Primary: Changes in mean reduction in IOP were comparable at one, two, three, and six months between latanoprost and dorzolamide/timolol. At one month, the mean reduction in IOP was 29.59% with latanoprost compared to 32.81% with dorzolamide/timolol (*P*=0.08). At two months, the mean reduction in IOP was 28.38% with latanoprost compared to 30.26% with dorzolamide/timolol (*P*=0.19). At three months, the mean reduction in IOP was 24.83% with latanoprost compared to 24.26% with dorzolamide/timolol (*P*=0.71). At six months, the mean reduction in IOP was 30.62% with latanoprost compared to 35.76% with dorzolamide/timolol (*P*=0.28). Secondary: Changes in mean reduction in IOP at 10 AM were comparable at one, two, three, and six months between latanoprost and dorzolamide/timolol. At one month, the mean reduction in IOP at 10 AM was 26.86% with latanoprost compared to 29.33% with dorzolamide/timolol (*P*=0.08). At two months, the mean reduction in IOP at 10 AM was 32.66% with latanoprost compared to 32.47% with dorzolamide/timolol (*P*=0.94). At three months, the mean reduction in IOP at 10 AM was 22.65% with latanoprost compared to 21.62% with dorzolamide/timolol (*P*=0.33). At six months, the mean reduction in IOP at 10 AM was 27.18% with latanoprost compared to 28.65% with dorzolamide/timolol (*P*=0.25). Rates of ocular adverse events did not differ significantly between latanoprost and dorzolamide (pooled RR, 0.96; 95% CI, 0.21 to 4.46; *P*=0.96). Latanoprost was associated with higher rates of conjunctival hyperemia compared to dorzolamide/timolol (6.2 vs 2.5%; RR, 2.38; 95% CI, 1.47 to 3.83; *P*=0.0004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Latanoprost was associated with higher rates of iris pigmentation compared to dorzolamide/timolol (2.7 vs 0.0%; RR, 8.11; 95% CI, 1.47 to 44.75; *P*=0.02). Dorzolamide/timolol was associated with higher withdrawal rates due to adverse events compared to latanoprost (4.0 vs 1.2%; RR, 0.34; 95% CI, 0.13 to 0.84; *P*=0.02). Dorzolamide/timolol was associated with higher rates of taste perversion compared to latanoprost (6.6 vs 0.2%; RR, 0.11; 95% CI, 0.04 to 0.26; *P*<0.00001).
Webers et al[41] Latanoprost 0.005% QPM and timolol 0.5% BID or latanoprost/timolol 0.005%/0.5%† QAM vs dorzolamide 2% BID to TID and timolol 0.5% BID or dorzolamide/timolol 2%/2% BID All patients had to complete a run-in phase of at least 2 weeks on timolol 0.5% BID monotherapy.	MA of 17 RCT's Over 85% of patients diagnosed with open- angle glaucoma or ocular hypertension	N=4,059 Duration varied from 1 to 3 months	Primary: Pooled change from baseline in IOP Secondary: Not reported	Primary: The absolute pooled mean change for dorzolamide/timolol, irrespective of concomitant or fixed, from baseline was -3.9 mm Hg (95% CI, -4.2 to -3.6) and -4.9 (95% CI, -5.2 to -4.6) at trough and peak, respectively. The relative change in IOP was -15.7% (95% CI, -17.2 to -14.3) and -20.1% (95% CI, -21.1 to -19.2) at trough and peak, respectively. Values for latanoprost were separated into concomitant and fixed use groups. The concomitant use of latanoprost and timolol 0gave an absolute pooled mean change from baseline of -6.0 (95% CI, -6.8 to -5.2) and relative change of -26.9% (-32.7 to -21.1). The fixed combination of latanoprost 0and timolol gave an absolute pooled mean change from baseline of -3.0 (95% CI, -3.8 to -2.2) and relative change of -13.4% (-16.0 to -10.8). Secondary: Not reported
Sonty et al[42] Dorzolamide/timolol 2.0%/0.5% one drop in the affected eye(s) BID vs	OL, PRO, XO Patients ages 18 years of age and older, with a clinical diagnosis of primary open angle	N=59 12 weeks	Primary: Reduction in IOP Secondary: Change in overall performance,	Primary: At visit one patients previously insufficiently controlled on latanoprost had a mean IOP of 22.2±2.4 mm Hg at eight hours and 21.4±2.5 mm Hg at 10 hours. At visit one, patients taking dorzolamide/timolol had a mean IOP 18.3±2.6 mm Hg at 10 hours, and at visit two which occurred at week four, and a mean

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>latanoprost 0.005% one drop in the affected eye(s) QPM</td><td>glaucoma, pigment-dispersion or exfoliation glaucoma, or ocular hypertension, IOP ≤31 mm Hg in both eyes, IOP 19 to 31 mm Hg in at least one eye, a visual acuity of at least 20/200 in each eye, and previous treatment with latanoprost dosed QPM for at least four consecutive weeks</td><td></td><td>typical daily activities, limitations of activities, compliance, satisfaction or quality of life as evaluated by the Comparison of Ophthalmic Medications for Tolerability Questionnaire, and adverse events</td><td>IOP 19.8±3.8 mm Hg at eight hours and 17.9±3.5 mm Hg at 10 hours at visit three which occurred at week 12.

After switching from latanoprost to dorzolamide/timolol the mean decrease at eight hours was -2.4±3.3 mm Hg and at 10 hours was -3.5±3.3 mm Hg (P<0.0001 for both).

Secondary:
No difference was seen between the two treatments with regards to overall performance, typical daily activities, limitations of activities, compliance, satisfaction or quality of life (P>0.05 for all).

A greater number of patients were found to have a higher frequency in burning and/or stinging and bitter taste when treated with dorzolamide/timolol (P>0.0001 for both), while unusual taste and itchy eyes were found to be associated with latanoprost (P=0.02 and P=0.05 respectively).

The most common adverse events reported by patients treated with dorzolamide/timolol were burning upon instillation and ocular hyperemia (P value not reported).</td></tr>
<tr><td>Coleman et al[43]

Dorzolamide/timolol 2%/0.5%1 drop into affected eye(s) BID

vs

bimatoprost 0.03% 1 drop into affected eye(s) QD</td><td>DB, MC, PRO, RCT

Diagnosis of open-angle glaucoma, ocular hypertension, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma, baseline IOP 22 to 34 mm Hg after at</td><td>N=177

3 months</td><td>Primary:
IOP at 8 AM and 10 AM at study visits occurring at one week, and one, two, and three months.

Secondary:
Assessment of safety and tolerability</td><td>Primary:
At 8 and 10 AM bimatoprost reduced IOP more than dorzolamide/timolol. The differences between the treatment groups were significant at all time points except for the three month, 10 AM measurement.

<table>
<tr><th colspan="6">Mean IOP (mm Hg) Change From Baseline</th></tr>
<tr><th>Time</th><th>Treatment Group</th><th>Week 1</th><th>Month 1</th><th>Month 2</th><th>Month 3</th></tr>
<tr><td rowspan="3">8 AM</td><td>Bimatoprost</td><td>-7.6</td><td>-7.1</td><td>-7.2</td><td>-6.8</td></tr>
<tr><td>Dorzolamide /timolol</td><td>-4.4</td><td>-4.8</td><td>-4.8</td><td>-5.0</td></tr>
<tr><td>P value</td><td><0.001</td><td><0.001</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="2">10 AM</td><td>Bimatoprost</td><td>-6.9</td><td>-6.5</td><td>-6.6</td><td>-6.4</td></tr>
<tr><td>Dorzolamide /timolol</td><td>-5.1</td><td>-5.1</td><td>-5.4</td><td>-5.6</td></tr>
</table></td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	least two weeks of topical timolol 0.5% therapy			<table><tr><td></td><td>*P* value</td><td><0.001</td><td>0.007</td><td>0.014</td><td>0.130</td></tr></table> Secondary: All reported adverse events were mild to moderate. Conjunctival hyperemia was reported more commonly in the bimatoprost group compared to the dorzolamide/timolol group (34.0 vs 17.2%; *P*=0.009). Ocular burning, ocular stinging, and taste perversion were the most common events in the dorzolamide/timolol group compared to the bimatoprost group (13.3 vs 2.0%; *P*=0.004, 9 vs 2%; *P*=0.025, 5 vs 0%; *P*=0.027).
Ikeda et al[44] Latanoprost QD vs betaxolol BID vs carteolol BID vs nipradilol† BID Dosing not specified for any of the regimens.	PRO, RCT, XO Patients were randomized to beta-adrenergic receptor antagonist therapy (betaxolol, carteolol, nipradilol) for 3 months, then switched to latanoprost for 3 months; patients with normal tension glaucoma, IOP ≤21 mm Hg, with evidence of glaucomatous changes in the visual field with optic nerve cupping, and absence of optic nerve neuropathies	N=60 6 months	Primary: IOP Secondary: IOP reduction rate, percent of non-responders in each treatment group (an IOP reduction rate ≤10%)	Primary: At three months, mean IOPs in the betaxolol, carteolol, and nipradilol groups were (mean±SD) 12.9±0.8, 12.4±0.6, and 12.9±0.8 mm Hg, respectively. After switching to latanoprost for three months, the mean IOPs were 11.7±0.8, 10.5±0.5, and 11.1±0.8, respectively, which all reached statistical significance (*P*<0.05). Secondary: At three months, the percent reductions in IOP with betaxolol, carteolol, and nipradilol were 10.8±4.7, 10.4±5.5, and 9.5±2.6%, respectively. After switching to latanoprost for three months, the percent reductions in IOP were 19.4±3.8, 24.1±4.3, 22.9±5.9%, respectively. Reductions with latanoprost compared to the betaxolol, carteolol, and nipradilol were all statistically significant (*P*<0.05). Beta-adrenergic receptor antagonists were associated with a significantly higher portion of non-responders compared to latanoprost (53.5 vs 20.9%; *P*=0.0257).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Erb et al[45] Tafluprost 0.0015% one drop in the affected eye(s) QD vs historical control (β adrenergic antagonist, CAI and PGA, alpha$_2$-adrenergic agonists, miotics, fixed combination therapy) Dosing not specified for any of the historical control regimens.	MC, OL, PRO Patients with glaucoma or ocular hypertension whom required a change of medication, an add-on therapy, or who were treatment naïve	N=661 6 to 12 weeks	Primary: Change from baseline in IOP after six to 12 weeks, tolerability and adverse events Secondary: Not reported	Primary: Overall, IOP was significantly reduced from 19.5±4.4 mm Hg at baseline to 16.4±2.9 mm Hg (*P*<0.001) with tafluprost after six to 12 weeks of treatment. Tafluprost was effective at lowering IOP across all prior monotherapy subgroups (treatment-naïve patients: 16.7±2.7 vs 22.6±3.9 mm Hg, β adrenergic antagonist: 16.7±2.6 vs 20.3±3.5 mm Hg, CAIs: 16.0±2.6 vs 19.0±3.6 mm Hg and PGAs: 15.8±2.6 vs 16.8±2.9 mm Hg; *P*<0.001 for all). After six to 12 weeks of treatment, an IOP of ≤18 mm Hg was achieved by 74.4% of patients switched to tafluprost, while 50.9 and 24.4% of these patients achieved IOP levels of ≤16 and ≤14 mm Hg, respectively (*P* values not reported). Following treatment with tafluprost, 85.7% of patients reported "very good" or "good" tolerability compared to 28.3% of patients at baseline. In patients previously treated with PGAs, tolerability was rated as "very good" or "good" by 39.6 and 46.3% of patients, respectively, compared to 1.3 and 8.3% of patients reporting this tolerability at baseline. Overall, 18 patients (0.8%) discontinued tafluprost due to adverse events, six patients (0.3%) discontinued due to lack of efficacy and four patients (0.2%) reported systemic side effects. Secondary: Not reported
Uusitalo et al[46] Tafluprost 0.0015% one drop in the affected eye(s) QD vs historical control (latanoprost 0.005%)	MC, OL, PRO Patients with primary open-angle glaucoma, capsular glaucoma or ocular hypertension in one or both eyes, previous treatment with latanoprost for ≥6 months and	N=158 12 weeks	Primary: Change from baseline in IOP, proportion of patients reporting adverse events Secondary: Not reported	Primary: The mean IOP was significantly lower with tafluprost treatment at weeks two (16.2 mm Hg; *P*=0.002), six (16.4 mm Hg; *P*=0.018) and 12 (16.4 mm Hg; *P*=0.049) compared to baseline treatment with latanoprost (16.8 mm Hg). After 12 weeks of treatment with tafluprost, there was a significantly lower incidence of abnormal symptoms in all of the following compared to baseline treatment with latanoprost: irritation/burning/stinging (28.4 vs 56.3%; *P*<0.001), foreign body sensation (27.1 vs 49.4%; *P*<0.001), tearing (27.1 vs 55.1%; *P*<0.001), itching (26.5 vs 46.8%; *P*<0.001), dry eye sensation (39.4 vs 64.6%; *P*<0.001), tear break-up time (71.6 vs 94.9%; *P*<0.001), corneal

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dosing not specified for the historical control regimens.	exhibiting ≥2 ocular symptoms, or one symptom and one sign of ocular surface irritation/ inflammation			fluorescein staining (40.6 vs 81.6%; *P*<0.001), conjunctival fluorescein staining (43.2 vs 84.2%; *P*<0.001), blepharitis (40.6 vs 60.1%; *P*<0.001), conjunctival hyperemia (60.0 vs 84.2%; *P*<0.001) and tear secretion/Schirmer's test (59.4 vs 71.5%; *P*=0.003). Secondary: Not reported
Traverso et al[47] Tafluprost 0.0015% one drop in the affected eye(s) QD at 8PM vs latanoprost 0.005% one drop in the affected eye(s) QD at 8PM	AC, DB, MC, PG, RCT Patients ≥18 years of age with primary open-angle glaucoma, exfoliation glaucoma, or ocular hypertension with an IOP 22 to 34 mm Hg in at least one eye	N=38 6 weeks	Primary: Reduction in IOP and duration of action by day 42 and 43 Secondary: IOP values at 8 AM on days seven, 21 and 42, proportion of patients reaching prespecified IOP reductions of ≥15%, ≥20%, ≥25% and ≥30% and overall adverse events	Primary: By day 42 of treatment, the mean diurnal values for tafluprost and latanoprost were comparable at 8 AM (17.1 vs 17.2 mm Hg), 12 noon (16.8 vs 15.7 mm Hg), 4 PM (17.4 vs 16.9 mm Hg) and 8 PM (17.4 vs 17.7 mm Hg), respectively. The mean change from baseline to 8 AM on day 42 was -9.7 mm Hg for tafluprost compared to -8.8 mm Hg for latanoprost. The estimated overall treatment difference in the change from baseline was 0.170 mm Hg (95% CI -1.268 to 1.608; *P*=0.811). The 8 AM measurement on day 43 (36 hours following the last dose) was the first time point where the increase in IOP was statistically significant, in comparison to the 8 AM measurement on day 42 (*P*<0.001) demonstrating a duration of effect of ≥24 hours. Secondary: The 8 AM IOP values were similar between patients treated with tafluprost or latanoprost on day seven (17.11 [-35.6%] vs 17.00 mm Hg [-32.9%]; *P* value not reported), day 21 (17.50 [-34.3%] vs 17.33 mm Hg [-32.3%]; *P* value not reported) and day 42 (17.14 [-35.9%] vs 17.17 mm Hg [-33.0%]; *P* value not reported). A similar proportion of patients treated with tafluprost and latanoprost, respectively, achieved a reduction in IOP from baseline ≥15% (88.9 vs 83.3%; *P*=1.00), ≥20% (77.8 vs 50.0%; *P*=0.164), ≥25% (55.6 vs 50.0%; *P*=1.00) and ≥30% (50.0 vs 44.4%; *P*=1.00). There were 17 adverse events in the tafluprost group compared to 23 events in the latanoprost group. Three adverse events were considered severe, all of which occurred in the tafluprost group (two photophobias and one report of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				eye pruritus). Best-corrected visual acuity did not differ between the treatment groups. No differences between the treatment groups were reported during the biomicroscopic examination. The ocular symptoms (irritation/burning/stinging, foreign body sensation, tearing, itching, photophobia dryness) were comparable between the treatment groups. Overall, 21.1% of patients in each treatment group reported drop discomfort. No variations in blood pressure or heart rate were reported in either group.
Uusitalo et al[48] Tafluprost 0.0015% one drop in the affected eye(s) QD at 8PM vs latanoprost 0.005% one drop in the affected eye(s) QD at 8PM	AC, DB, MC, NI, PG, RCT Patients ≥18 years of age with primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension and an untreated IOP 22 to 34 mm Hg in at least one eye	N=533 104 weeks	Primary: Change from baseline in diurnal IOP, adverse events and ocular safety Secondary: Not reported	Primary: After 24 months of treatment, the mean reduction from baseline in IOP was 7.1 mm Hg (-29.1%) in the tafluprost group compared to 7.7 mm Hg (-32.2%) in the latanoprost group. The upper limit of the 95% CI was 1.38 mm Hg, within the NI limit of 1.5 mm Hg. Over 24 months, at least one adverse event was reported by 66.7% of patients in the tafluprost group compared to 61.4% of patients in the latanoprost group. The most frequently reported adverse events in the tafluprost and latanoprost groups, respectively, were eyelash growth (6.4 vs 4.2%), eye irritation (5.2 vs 5.3%), eyelash discoloration (4.8 vs 3.8%), eye pain (5.6 vs 2.7%) and ocular hyperemia (5.3 vs 2.7%). None of the differences in adverse events between treatment groups were statistically significant (*P*>0.05 for all). In general, the LogMAR scores for best-corrected visual acuity were stable throughout the study in both groups. A change from baseline of >0.2 LogMAR occurred in 11.4% tafluprost-treated patients compared to 14% of patients who received latanoprost. No differences in conjunctival redness scores were reported between treatments (*P*=0.830). The results from biomicroscopic examinations of the lid, conjunctiva, cornea, anterior chamber, iris and lens for both eyes were comparable between the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Amongst patients treatment naïve to prostaglandins, there was a higher incidence of severe iris pigmentation in the latanoprost group; however, the difference after 24 months was not statistically significant (*P*=0.848). The overall incidence of drop-discomfort was low in both groups with approximately 75 to 80% of patients free from discomfort (*P*=0.402). There were no significant changes in visual field findings at 24 months in either treatment group. Moreover, there were no significant changes in blood pressure or heart rate during the study. Secondary: Not reported
Konstas et al[49] Tafluprost 0.0015% one drop in the affected eye(s) QD at 8PM vs latanoprost 0.005% one drop in the affected eye(s) QD at 8PM	AC, PRO, RCT, SB, XO Adults 39 to 85 years of age with primary open-angle glaucoma or ocular hypertension (untreated sitting morning IOP of 24 to 33 mm Hg in the study eye on two separate baseline IOP) and CCT between 500 and 600 µm	N=40 XO at 3 months, 6 months total	Primary: Mean 24 hour IOP Secondary: IOP at individual time points, peak, trough and fluctuations in 24 hour IOP	Primary: Patients treated with tafluprost experienced a similar mean 24 hour IOP compared to patients treated with latanoprost (17.8±2.2 vs 17.7±2.1 mm Hg; *P*=0.417). Secondary: There were no statistically significant differences between the treatment groups with regard to IOP at individual time points (*P*≥0.372 for all time points). Patients in the tafluprost treatment group demonstrated significantly lower 24 hour IOP fluctuation compared to the latanoprost group (3.2±1.7 vs 3.8±1.8 mm Hg; *P*=0.008). Conversely, latanoprost treatment was associated with a significantly lower 24 hour trough IOP (15.9±2.1 vs 16.3 ±2.2 mm Hg; *P*=0.041). There was no significant difference in 24 hour peak IOP between the latanoprost and tafluprost treatment groups (19.7 vs 19.5 mm Hg, respectively; *P*=0.277).
Schnober et al[50] Tafluprost 0.0015% one	AC, DB, RCT, XO Patients ≥21 years	N=51 XO at week 6,	Primary: Mean IOP at 8 PM	Primary: After six weeks of treatment, the mean reduction in IOP at 8 PM was greater with travoprost compared to tafluprost (7.2 vs 6.6 mm Hg; *P*=0.01). Patients

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>drop in the affected eye(s) QD at 8 PM

vs

travoprost 0.004% one drop in the affected eye(s) QD at 8 PM</td><td>of age with primary open-angle glaucoma or ocular hypertension in at least one eye; patients on IOP-lowering therapy had to have an IOP >21 mm Hg in at least one eye at 8 AM, ≥19 mm Hg in the same eye at 4 PM, and, <35 mm Hg in both eyes at all diurnal time points</td><td>12 weeks total</td><td>Secondary:
Solicited symptom survey questions, hyperemia, and visual acuity</td><td>treated with travoprost experienced a significantly greater reduction in IOP compared to tafluprost at 10 AM (P=0.02), 12 noon (P=0.01), 4 PM (P=0.01), 6 PM (P<0.01), but not at 8 AM (P=0.06) or 2 PM (P=0.09).

Secondary:
There were no significant differences between tafluprost and travoprost treatments with regard to individual symptom scores (P>0.05 for all)

Investigator-observed hyperemia scores were significantly increased from baseline in both travoprost (0.26; P<0.01) and tafluprost groups (0.42; P<0.01), although the increase with travoprost therapy was significantly smaller than with tafluprost (P<0.01).

There was no significant change in visual acuity between the travoprost and tafluprost treatment groups (P=0.49).

No difference in patient tolerability was reported between the two groups (P=0.18)</td></tr>
<tr><td>Walters et al[51]

Levobunolol 0.5% one drop into the affected eye(s) BID

vs

timolol GFS 0.5% one drop into the affected eye(s) with placebo QD</td><td>DB, MC, RCT, XO

Patients 18 years of age and older, with open angle glaucoma or ocular hypertension, with a morning IOP of at least 22 mm Hg in one or both eyes after a 3 week washout period</td><td>N=152

12 week (6 weeks of treatment followed by XO to 6 weeks of treatment with alternative medication)</td><td>Primary:
Change in IOP from baseline

Secondary:
Heart rate and adverse events</td><td>Primary:
<table>
<tr><th colspan="5">IOP Change from Baseline</th></tr>
<tr><th></th><th colspan="2">Peak IOP (mm Hg)</th><th colspan="2">Trough IOP (mm Hg)</th></tr>
<tr><th></th><th>Levo-bunolol</th><th>Timolol GFS</th><th>Levo-bunolol</th><th>Timolol GFS</th></tr>
<tr><td>Baseline</td><td>24.3±0.39</td><td>24.3±0.39</td><td>26.4±0.38</td><td>26.4±0.38</td></tr>
<tr><td>End of Study Period</td><td>19.6±0.31</td><td>19.3±0.29</td><td>20.2±0.29</td><td>20.3±0.28</td></tr>
<tr><td>Change From Baseline</td><td>-4.7±0.34</td><td>-5.0±0.33</td><td>-6.2±0.32</td><td>-6.1±0.33</td></tr>
</table>
The between group difference in peak IOP was -0.3 mm Hg (95% CI, -0.6 to 0.2; P=0.34) and no change was seen with regards to trough IOP (95% CI, -0.5 to 0.4; P=0.89).

Secondary:
Both levobunolol and timolol GFS lowered heart rate, however the timolol GFS group affected heart rate significantly less (P=0.001).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly more patients in the timolol GFS group experienced an adverse event related to the treatment drug as compared to the levobunolol group (29 vs 17%; *P*=0.012). Blurred vision was also experienced by significantly more patients in the timolol GFS group when compared to the levobunolol group (8 vs 1%; *P*=0.013).
Safety/Adverse Events				
Honrubia et al[52] Bimatoprost 0.03% one drop in the affected eye(s) QD vs latanoprost 0.005% one drop in the affected eye(s) QD vs travoprost 0.004% one drop in the affected eye(s) QD	MA of 13 RCTs Adults ≥18 years of age with ocular hypertension and/or glaucoma	N=2,222 Duration varied with an average period follow up of 4.1 months	Primary: Incidence of conjunctival hyperemia Secondary: Not reported	Primary: The proportion of patients who developed conjunctival hyperemia was 40.2, 16.5 and 33.0% in the bimatoprost, latanoprost and travoprost groups, respectively. Treatment with latanoprost was associated with a lower incidence of conjunctival hyperemia compared to bimatoprost (OR, 0.32; 95% CI, 0.24 to 0.42; *P*<0.00001). Treatment with latanoprost was associated with a lower incidence of conjunctival hyperemia compared to travoprost (OR, 0.51; 95% CI, 0.39 to 0.67; *P*<0.00001). The proportion of patients who developed conjunctival hyperemia with bimatoprost and travoprost was not directly compared. Secondary: Not reported
Hedner et al[53] Latanoprost 0.005% one drop in both eyes QD vs placebo one drop in both eyes QD	DB, PC, RCT, XO Patients ≥18 years of age with asthma and no exacerbations in three months prior to enrollment, FEV_1 70 to 90% of predicted, 10% reversibility of FEV_1	N=24 Two six-day treatment periods separated by a two week washout	Primary: Mean morning peak expiratory flow volume Secondary: Mean evening peak expiratory flow volume, methacholine provocation	Primary: The difference in mean morning peak expiratory flow volume between the latanoprost and placebo groups was not significant (-1.4 L/minute; 95% CI, -11.2 to 8.3; *P*=0.76). Secondary: The difference in mean evening peak expiratory flow volume between the latanoprost and placebo groups was not significant (1.9 L/minute; 95% CI, -9.2 to 13.0; *P* value not reported). Changes in FEV_1 after 50 and 200 µg/mL methacholine provocation tests

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	after inhalation of albuterol		tests, and albuterol use	with latanoprost treatment compared to corresponding placebo treatment were judged to be clinically irrelevant. In general, no or only mild-to-moderate daytime asthma symptoms were reported. Adverse events were few and evenly distributed, including respiratory tract infection and headache.
Janulevičiene et al[54] Tafluprost 0.0015% one drop in the affected eye(s) QD vs historical control (latanoprost 0.005%) Dosing not specified for the historical control regimens.	PRO, SB Patients ≥18 years of age with open-angle glaucoma in at least one eye and at least mild dry eye according to OSDI score and/or corneal fluorescein staining in at least one eye, IOP controlled with latanoprost within previous month	N=30 12 weeks	Primary: Tear film osmolarity level Secondary: IOP-lowering effect, tear film break-up time, OSSG and OSDI	Primary: Compared to baseline, the mean tear osmolarity was significantly decreased two, six and 12 weeks after initiating tafluprost to 308.0 mOsm/L (*P*=0.002), 301.7 mOsm/L (*P*<0.001) and 302.0 mOsm/L (*P*<0.001), respectively. Secondary: Compared to baseline treatment with latanoprost, IOP remained unchanged at week two (16.3 mm Hg; *P*=0.651), week six (16.2 mm Hg; *P*=0.673) and 12 weeks (16.3 mm Hg; *P*=0.820) after changing medication from latanoprost to tafluprost. The mean tear film break-up time increased significantly from 3.7 seconds at baseline to 4.1 seconds after two weeks, 5.2 seconds after six weeks and 6.5 seconds after 12 weeks. Forty-five eyes (75.0%) showed abnormal fluorescein staining of the cornea at baseline. The number of eyes with abnormal values decreased during the course of the study to 35 (58.3%), 21 (35.0%), and seven eyes (11.7%) at weeks two, six and 12, respectively. The results of the OSDI questionnaire demonstrated a lower incidence of mild dry eye complaints after 12 weeks of tafluprost treatment (26.7 vs 53.3%; *P* value not reported). Results of the OSSG questionnaire revealed that 40.0% of patients felt dry eye symptoms some of the time at baseline, compared to 26.7% of patients reporting these symptoms 12 weeks after initiating tafluprost (*P* value not reported).
Lewis et al[55] Travoprost 0.004% with benzalkonium chloride one	DB, MC, PG, RCT Adult patients with open-angle	N=690 3 months	Primary: Equivalence of IOP taken at 8 AM, 10 AM and	Primary: The combined mean IOP difference between travoprost with benzalkonium chloride and travoprost without benzalkonium chloride was 0.0 mm Hg at 8 AM (95% CI, -0.4 to 0.4; *P*=0.8831), 0.0 mm Hg at 10 AM (95% CI, -0.4 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
drop in the affected eye(s) QPM vs travoprost 0.004% without benzalkonium chloride one drop in the affected eye(s) QPM	glaucoma or ocular hypertension		9 PM at two, six and 12 weeks Secondary: Adverse events	0.4; *P*=0.9501) and 0.1 mm Hg at 4 PM (95% CI, -0.3 to 0.5; *P*=0.7003). Secondary: Ocular hyperemia was the most common treatment-related adverse event reported and occurred in 6.4% of patients treated with travoprost without benzalkonium chloride and 9.0% of patients treated with travoprost with benzalkonium chloride (*P* value not reported). No serious adverse events were reported during the study.
Henry et al[56] Travoprost 0.004% without benzalkonium chloride one drop in the affected eye(s) QPM vs historical control (bimatoprost 0.03% or latanoprost 0.005%) Dosing not specified for any of the historical control regimens.	MC, OL, PRO Patients with open-angle glaucoma or ocular hypertension who were unable to tolerate latanoprost or bimatoprost, or who were judged by their clinician to be good candidates for travoprost benzalkonium chloride-free solution	N=691 12 weeks	Primary: Change in ODSI scores Secondary: IOP, conjunctival hyperemia grading and adverse events	Primary: Patients previously treated with latanoprost showed a statistically significant improvement in OSDI score from 12.0 at baseline to 8.7 at week 12 after switching to travoprost (*P*<0.0001). Patients previously treated with bimatoprost showed a statistically significant improvement in OSDI score from 13.2 at baseline to 8.7 at week 12 after switching to travoprost (*P*<0.0001). Individual questions on the ODSI index that were significantly improved with tafluprost included sensitivity to light, gritty feeling, painful eyes, blurred vision, poor vision, reading difficulties, driving difficulties at night, working with the computer, windy conditions and low humidity (*P*≤0.0007). Secondary: A significant decrease in IOP was observed following a switch from latanoprost to travoprost (*P*<0.001), but not from bimatoprost to travoprost (*P*=0.5245). Patients previously treated with bimatoprost or latanoprost experienced a significant decrease in hyperemia severity grading at week 12 following a switch to tafluprost (*P*<0.001). Commonly reported adverse events with travoprost were conjunctival hyperemia (6%) and change in visual acuity (4%). The results from a patient preference survey reported that 72.4% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				preferred travoprost compared to 27.6% who preferred their previous therapy (*P*<0.001).

*Agent not currently available in the United States.
† Strength not currently available in the United States.
Drug regimen abbreviations: BID=twice daily, QAM=once daily in the morning, QD=once daily, QPM=once daily at night, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blind, SR=systematic review, XO=crossover
Miscellaneous abbreviations: CCT=central corneal thickness, FEV_1=forced expiratory volume in 1 second, GFS=gel forming solution, IOP=intraocular pressure, logMAR=logarithm of the minimum angle of resolution, mm Hg=millimeters of mercury, OSDI=ocular surface disease index, OSSG=ocular surface symptoms in glaucoma, SD=standard deviation, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[9-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Bimatoprost	No differences in safety or efficacy have been observed between elderly and younger patients. Use in pediatric patients <16 years is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use.	Not reported	No adverse effects seen after 48 months.	C	Unknown
Latanoprost	No differences in safety or efficacy have been observed between elderly and younger patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown
Tafluprost	No differences in safety or efficacy have been observed between elderly and younger patients. Not recommended for pediatric use due to potential safety concerns related to increased pigmentation following chronic use.	Not reported	Not reported	C	Unknown
Travoprost	No differences in safety or efficacy have been observed between elderly and younger patients. Use in pediatric patients <16 years is not recommended due to potential safety concerns related to increased pigmentation following long term chronic use.	No dose adjustment required.	No dose adjustment required.	C	Unknown

Adverse Drug Events

Table 6. Adverse Drug Events[9-12]

Adverse Events	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Cardiovascular				
Bradycardia	-	-	-	1 to 5
Chest pain/angina pectoris	-	1 to 2	-	1 to 5
Hypertension	-	-	-	1 to 5
Hypotension	-	-	-	1 to 5
Central Nervous System				
Anxiety	-	-	-	1 to 5
Depression	-	-	-	1 to 5
Headache	1 to 5	-	6	1 to 5
Gastrointestinal				
Dyspepsia	-	✔	-	1 to 5
Gastrointestinal disorder	-	-	-	1 to 5
Musculoskeletal				
Arthritis	-	-	-	1 to 5
Asthenia	1 to 5	-	-	-
Muscle, joint, back pain	-	1 to 2	-	1 to 5
Ocular				
Abnormal vision	-	-	-	1 to 4
Allergic conjunctivitis	<10	-	5	-
Asthenopia	<10	-	-	-
Blepharitis	<10	-	-	1 to 4
Blurred vision	-	5 to 15	2	1 to 4
Burning/stinging	<10	5 to 15	7	-
Cataract	<10	-	3	1 to 4
Conjunctival edema	<10	-	-	-
Conjunctival hyperemia	25 to 45	5 to 15	4 to 20	30 to 50
Conjunctivitis	-	-	5	1 to 4
Corneal edema	-	✔	-	-
Corneal staining	-	-	-	1 to 4
Decreased visual acuity	-	-	-	5 to 10
Dryness/dry eye	<10	1 to 4	3	1 to 4
Eye discharge	<10	-	-	-
Eye discomfort	-	-	-	5 to 10
Eye disorder	-	-	-	1 to 4
Eye pain	<10	1 to 4	3	5 to 10
Flare	-	-	-	1 to 4
Foreign body sensation	<10	5 to 15	-	5 to 10
Herpes keratitis	-	✔	-	-
Increased eyelash growth	>10	✔	-	✔
Increased eyelash pigmentation	<10	✔	2	✔
Increased iris pigmentation	<10	5 to 15	-	1 to 4
Increased periocular skin pigmentation	<10	✔	-	✔
Iritis	<1	✔	-	-
Keratitis	-	✔	-	-
Lid crusting	-	1 to 4	-	1 to 4
Lid discomfort/pain	-	1 to 4	-	-
Lid edema	-	1 to 4	-	-
Lid erythema	<10	1 to 4	-	-
Macular edema	✔	✔	-	-

Adverse Events	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Ocular irritation	<10	-	-	-
Ocular pruritus	>10	5 to 15	5	5 to 10
Photophobia	<10	1 to 4	-	1 to 4
Subconjunctival hemorrhage	<10	-	-	1 to 4
Superficial punctate keratitis	<10	5 to 15	-	1 to 4
Tearing	<10	1 to 4	-	1 to 4
Visual disturbance	<10	-	-	-
Respiratory				
Asthma exacerbation	-	✔	-	-
Bronchitis	-	-	-	1 to 5
Common cold	10	-	4	-
Cough increased	-	-	3	-
Sinusitis	-	-	-	1 to 5
Miscellaneous				
Abnormal liver function tests	1 to 5	-	-	-
Abnormal hair growth	<10	-	-	-
Accidental injury	-	-	-	1 to 5
Hypercholesterolemia	-	-	-	1 to 5
Infection	10	4	-	1 to 5
Prostate disorder	-	-	-	1 to 5
Rash, allergic reaction	-	1 to 2	-	1 to 5
Toxic epidermal necrolysis	-	✔	-	-
Urinary incontinence	-	-	-	1 to 5
Urinary tract infection	-	-	2	1 to 5

Contraindications

Table 7. Contraindications[9-12]

Contraindication	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Known hypersensitivity to the active ingredient or benzalkonium chloride	-	✔	-	-

Warnings/Precautions

Table 8. Warnings and Precautions[9-12]

Warning/Precaution	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Bacterial keratitis; cases have been reported following treatment with multiple-dose containers of this product	✔	✔	-	✔
Contact lens use; remove contacts prior to instillation and reinsert 15 minutes following administration	✔	✔	-	✔
Eye lash changes; gradual changes including increased length, thickness and number of lashes may be reversible upon discontinuation of treatment	✔	✔	✔	✔
Has not been evaluated for treatment in patients with angle-closure, inflammatory or neovascular glaucoma	✔	✔	-	✔
Intraocular inflammation; use caution in patients with intraocular inflammation as inflammation may be exacerbated with prostaglandin analogue treatment	✔	✔	✔	✔

Warning/Precaution	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Macular edema; use with caution in aphakic patients, pseudophakic patients with a torn posterior lens or in patients with known risk factors for macular edema	✔	✔	✔	✔
Pigmentation; ophthalmic prostaglandin analogues have been reported to cause permanent changes to pigmented tissues	✔	✔	✔	✔

Drug Interactions

Bimatoprost solution formulated as the branded product Latisse® should be used with caution in patients using ophthalmic prostaglandin analogues for the treatment of elevated intraocular pressure. Concomitant use may interfere with the desired reduction in intraocular pressure.[57]

In vitro studies have shown that administration of latanoprost with eye drops containing thimerosal may result in precipitate formation. Use of these agents should be separated by at least five minutes.[10]

Dosage and Administration

Table 9. Dosing and Administration[9-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Bimatoprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension: Ophthalmic solution: instill one drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily	Use in pediatric patients <16 years is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use.	Ophthalmic solution: 0.01% (2.5, 5, 7.5 mL) 0.03% (2.5, 5, 7.5 mL)
Latanoprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension: Ophthalmic solution: instill one drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily	Safety and efficacy in children have not been established.	Ophthalmic solution: 0.005% (2.5 mL)
Tafluprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension: Ophthalmic solution: instill one drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily	Not recommended for pediatric use due to potential safety concerns related to increased pigmentation following chronic use.	Ophthalmic solution: 0.0015% (30 or 90 0.3 mL single-use containers)
Travoprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension: Ophthalmic solution: instill one drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily	Use in pediatric patients <16 years is not recommended due to potential safety concerns related to increased pigmentation following long term chronic use.	Ophthalmic solution: 0.004% (2.5, 5 mL)

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Glaucoma Panel, Preferred Practice Patterns Committee. Primary Open-Angle Glaucoma (2010)**[2]	Medical management • Unless contraindicated, medical therapy is the most common initial intervention to lower intraocular pressure (IOP). • Medication choice may be influenced by potential cost, side effects and dosing schedules. • Patient adherence to therapy is enhanced by using eye drops with the fewest side effects as infrequently as necessary to achieve the target IOP. • If target IOP is not achieved by one medication, additional medications, combination therapies, or switching of treatments may be considered to reach the target IOP. • Ophthalmic formulations of β adrenergic antagonists and prostaglandin analogs are most frequently used to lower IOP. • Prostaglandin analogs are the most effective IOP-lowering drugs and can be considered as initial medical therapy unless cost, side effects or intolerance preclude their use. • Alpha$_2$-adrenergic agonists, ophthalmic and oral carbonic anhydrase inhibitors and parasympathomimetics are less frequently used. • If a drug fails to reduce IOP despite adherence to treatment, it should be replaced with an alternative agent until effective medical treatment is achieved. • If a single medication effectively reduces IOP but the target IOP has not been achieved, combination therapy or switching to an alternative medication should be considered. • Laser trabeculectomy is an alternative for patients who cannot or will not use medications reliably due to cost, memory problems, difficulty with instillation, or intolerance to the medication. • Filtering surgery is an alternative after medications and laser trabeculectomy. • Cyclodestructive surgery is reserved for patients with reduced visual acuity and patients who are poor candidates for incision surgery.
American Optometric Association: **Clinical Practice Guidelines: Care of the Patient with Open-Angle Glaucoma (2010)**[8]	Treatment options • Glaucoma treatment begins with pharmacological intervention, proceeding to laser therapy and surgery when necessary. • Treatment of open-angle glaucoma includes the use of topical or orally administered agents to enhance aqueous outflow, reduce aqueous production or both. Prostaglandin analogs • Latanoprost 0.005% lowers IOP by up to 35% when administered once daily and is at least as effective as timolol maleate in lowering IOP. It has additive effects when administered with other agents. • Bimatoprost 0.03% has a similar effectiveness to latanoprost. It reduces IOP up to 33%. • Travoprost 0.004% has a similar effectiveness to latanoprost. It reduces IOP up to 33%. Travoprost may be more effective than other active agents in lowering IOP in African Americans. Epinephrine compounds • Epinephrine is not as effective as other drugs in lowering IOP and their use is relatively rare.

Clinical Guideline	Recommendations
	• An epinephrine prodrug, dipivefrin, is available in a 0.1% concentration and is the drug of choice among epinephrine products. The lower concentration of dipivefrin is equivalent in effectiveness to a 1 to 2% concentration of epinephrine, has better penetration of the cornea and reduced side effects. Alpha$_2$-adrenergic agonists • Apraclonidine lowers IOP by 25% and prevents the acute spike in IOP that may occur after argon laser trabeculoplasty and other laser procedures. • Apraclonidine is also effective in minimizing IOP increases after cycloplegia in patients with glaucoma. • Apraclonidine 0.05% is as efficacious as 0.5% timolol used twice daily. It may also have additive effects with timolol in lowering IOP and may be valuable for patients resistant to further reduction in IOP. • Brimonidine is more selective than apraclonidine for alpha$_2$- receptors. Brimonidine 0.2% reduces IOP up to 27%, without tachyphylaxis. When used twice a day, it is more effective than betaxolol and similar to timolol. As monotherapy, brimonidine is less effective than prostaglandin analogs but additive with timolol and latanoprost and can be used as combination or replacement therapy. β adrenergic antagonists • Timolol, carteolol, levobunolol, metipranolol and betaxolol (suspension) are unique β adrenergic antagonist preparations for treating glaucoma. The doses of β adrenergic antagonists used in treating glaucoma range from 0.25 to 1.0%, and are dosed once or twice daily. • Betaxolol may cause fewer pulmonary and cardiovascular side effects, but is less effective at lowering IOP compared to timolol, carteolol, levobunolol, and metipranolol. Carbonic anhydrase inhibitors • Acetazolamide is available as an injection or sustained-release capsules. • This class lowers IOP by 20 to 40%, but they are poorly tolerated. The most effective doses are 500 mg of acetazolamide once or twice daily and 50 mg of methazolamide two to three times daily. • Dorzolamide hydrochloride lowers IOP by 3 to 5 mm Hg. As adjunctive therapy, dorzolamide is approximately equivalent to 2% pilocarpine in further lowering IOP. • Brinzolamide is equal to dorzolamide in IOP-lowering effects. Both have additive effects when used with timolol. Miotic agents • Pilocarpine is the miotic drug most frequently in glaucoma in doses ranging from 1 to 4%; the duration of action is at least six hours. • Pilocarpine also is available in a 4% gel preparation. Combination treatment: • Studies support the rationale for combining separate topical glaucoma medications into a single formulation to decrease the number of applications per day, thereby increasing compliance. • Results from clinical studies demonstrate that combination treatment is more effective in reducing IOP compared to monotherapy with either agent alone.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td>National Institute for Clinical Excellence: Glaucoma: Diagnosis and Management of Chronic Open- Angle Glaucoma and Ocular Hypertension (2009)[3]</td><td>
<u>Medication selection for patients with ocular hypertension, suspected open-angle glaucoma, or open-angle glaucoma</u>
• Patient comorbidities, possible drug interactions, and preservative allergies should be factored into medication selection.
• First-line medication therapy should consist of ophthalmic β adrenergic antagonists or ophthalmic prostaglandin analogs.
• Carbonic anhydrase inhibitors and ophthalmic sympathomimetics should be considered second line medication therapy.
• Pharmacological treatment should be switched to another class (ophthalmic β adrenergic antagonist, ophthalmic carbonic anhydrase inhibitor, ophthalmic prostaglandin analogs or ophthalmic sympathomimetic) when intolerance to current medication is experienced or target IOP reduction has not been achieved.
• Additional agents can be added when target IOP has not been achieved with a single agent.
• Eye drop instillation technique should be assessed when IOP does not decrease with medication therapy.

<u>Treatment of ocular hypertension or suspected open-angle glaucoma</u>
• Patients diagnosed with ocular hypertension or suspected open-angle glaucoma should be offered medication based on the risk factors of measured IOP, measured central corneal thickness, and age (see chart below).
• Patients should be referred to an ophthalmologist when target IOP reduction cannot be achieved.

<table>
<tr><td>Central Corneal Thickness</td><td colspan="2">More than 590 micrometers</td><td colspan="2">555 to 590 micrometers</td><td colspan="2">Less than 555 micrometers</td><td>Any</td></tr>
<tr><td>Untreated IOP (mm Hg)</td><td>>21 to 25</td><td>>25 to 32</td><td>>21 to 25</td><td>>25 to 32</td><td>>21 to 25</td><td>>25 to 32</td><td>>32</td></tr>
<tr><td>Age (Years)</td><td>Any</td><td>Any</td><td>Any</td><td>Treat until 60</td><td>Treat until 65</td><td>Treat until 80</td><td>Any</td></tr>
<tr><td>Treatment</td><td>None</td><td>None</td><td>None</td><td>Beta-blocker*</td><td>Prosta-glandin analogs</td><td>Prosta-glandin analogs</td><td>Prosta-glandin analogs</td></tr>
</table>
*If beta-blockers are contraindicated offer a prostaglandin analogue.

<u>Treatment of patients with open-angle glaucoma</u>
• Ophthalmic prostaglandin analogs should be offered to new patients diagnosed with early or moderate open-angle glaucoma at risk of significant vision loss and patients with advanced open-angle glaucoma who are scheduled for surgery.
• Pharmacological treatment for elevated IOP should continue until progression of optic nerve head damage, progression of visual field defect or reported intolerance to current medication.
• Patients should be offered surgery along with medication if they are at risk for vision loss despite treatment.
• If a patient's IOP has not lowered after surgery, the following should be considered: pharmacological treatment with ophthalmic agents (β adrenergic antagonist, carbonic anhydrase inhibitor, prostaglandin analogs, or sympathomimetic), further surgery with pharmacological augmentation or laser trabeculoplasty or cyclodiode laser treatment.
• Patients who are not candidates for surgery or prefer not to have surgery should be offered pharmacological treatment with ophthalmic agents (β
</td></tr>
</table>

Clinical Guideline	Recommendations
	adrenergic antagonist, carbonic anhydrase inhibitor, prostaglandin analogs, or sympathomimetic), laser trabeculoplasty or cyclodiode laser treatment.

Conclusions

Four ophthalmic prostaglandin analogues are currently available in the United States including bimatoprost (Lumigan®), latanoprost (Xalatan®), tafluprost (Zioptan®) and travoprost (Travatan Z®). All are Food and Drug Administration (FDA)-approved for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[9-12] All agents in this class are administered once daily, and only latanoprost is available generically.[13] In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter two are most notable if only one eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma. Tafluprost is the only agent within the class that is formulated as preservative-free and may be associated with less ocular irritation compared to the other ophthalmic prostaglandin analogues.[12,49] Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues and is available as both a 0.01% and 0.03% ophthalmic solution.[9,14,16,18,19,21,28,29] Study results have demonstrated statistically significant differences in IOP-lowering ability among the other agents in the class; however, the differences are generally small and the clinical significance of these differences has not been established.

Current clinical guidelines by the American Academy of Ophthalmology and the American Optometric Association both support the use of ophthalmic β adrenergic antagonists or ophthalmic prostaglandin analogues as initial medical therapy to lower IOP and reduce the risk of progression to visual field loss or optic disc changes in patients with elevated IOP.[2,3,8] Guidelines do not recommend one ophthalmic prostaglandin analogue over another. The results from various meta-analyses have demonstrated that prostaglandin analogues reduce IOP by up to 35% and to a further extent compared to alpha$_2$-adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors and other recommended therapies.[16] Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory.

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