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, but 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 both bimatoprost and latanoprost formulations. The BAK-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). Latanoprost is the only agent that is currently available generically. The most frequently reported adverse events associated with the ophthalmic prostaglandin analogues include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.[1-5] All of the agents within the class have been shown to reduce IOP from baseline values by ≥30%.[8]

Table 1. Current Medications Available in the 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%, 0.03%	-
Latanoprost (Xalatan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.005%	✔
Tafluprost (Zioptan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.0015%	-
Travoprost (Travatan Z®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.004%	-

Evidence-based Medicine

- In one study (N=38) the reduction in IOP from baseline did not differ significantly between patients receiving tafluprost compared to latanoprost over six weeks (difference: 0.170 mm Hg; 95% 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 and no differences in adverse events were reported between the two treatments (*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 from a meta-analysis of eight studies 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 of 28 studies, 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 of 42 studies show that the prostaglandin analogues were 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 month (-27.2 vs -21.2%; *P* value not reported) and month three (-28.8 vs -22.2%; *P* value not reported).[16]
- In a randomized controlled study, treatment with latanoprost was associated with greater reductions in IOP compared to treatment with 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 ophthalmic timolol *(P*<0.001)[18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - 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.[19]
    - 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.[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 and sympathomimetic) when medication intolerance to current medication is experienced or target intraocular pressure (IOP) reduction has not been achieved.[8,19-20]

- Other Key Facts:
    - Latanoprost is the only ophthalmic prostaglandin analogue that is available generically. Generic formulations of bimatoprost and travoprost are expected in early 2015.[5]
    - Tafluprost is the only preservative-free ophthalmic prostaglandin product and is only available in sing-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]
    - All of the ophthalmic prostaglandins are dosed once daily in the evening.[1-4]

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Therapeutic Class Review
Ophthalmic Prostaglandin Analogues

Overview/Summary

There are currently four ophthalmic prostaglandin analogues approved by the Food and Drug Administration (FDA) for the treatment of glaucoma, including bimatoprost (Lumigan®), latanoprost (Xalatan®), tafluprost (Zioptan®) and travoprost (Travatan Z®).[1-4] The ophthalmic prostaglandin analogues are believed to reduce intraocular pressure (IOP) by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.[1-5] Glaucoma is the leading cause of irreversible blindness and second leading cause of vision loss in the world. While, the most common type of glaucoma is primary open-angle, other distinct types include, acute angle-closure, secondary and congenital.[6] Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness.

The one major risk factor for glaucoma that is treatable is IOP. Evidence shows that reducing IOP inhibits the progression of optic nerve damage and visual field loss.[7-8] Patients with an elevated IOP may receive treatment even if no visual field loss or optic nerve damage is present. An IOP of greater than 22 mm Hg is typically considered to be elevated and would be treated by most clinicians, but this number varies according to screening methods, risk factors and disease progression. The target IOP should be individualized based on response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[9-11] Treatment of glaucoma currently focuses on decreasing IOP by one of three methods: laser therapy, surgery, or medical intervention.[9-11] Medical intervention includes five ophthalmic classes of drugs used for the long-term management of glaucoma: alpha$_2$-adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics, and prostaglandin analogues. Parasympathomimetics and prostaglandin analogues increase aqueous outflow, while β adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha$_2$-adrenergic agonists decrease aqueous humor formation and increase its outflow.[5,12]

All of the ophthalmic prostaglandin analogues are administered once daily. 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), which is used in both bimatoprost and latanoprost formulations. The BAK-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). Currently the only generic product within the class is latanoprost. Generic formulations of bimatoprost and travoprost are expected to be available in the first half of 2015.[16] The most frequently reported adverse events associated with these agents include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.[1-5,13]

Current consensus guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line medication therapy in patients with elevated IOP. Combination or monotherapy with agents from another class is recommended in patients that experience intolerable side effects or who do not achieve goal IOP reductions with first-line agents.[9-11] The ophthalmic prostaglandin analogues are the most effective drugs in lowering IOP. Meta-analyses have reported 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.[14-15]

Medications

Table 1. Medications Included Within Class Review[1-4]

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

Indications

Table 2. Food and Drug Administration-Approved Indications[1-4]

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

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,12]

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 studies 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.[16-56]

Of the four ophthalmic prostaglandin analogues, bimatoprost appears to have the greatest efficacy in reducing IOP; however, studies have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost.[14-15,17-18,21,24,26-27,30-31] Available studies suggest that the newest agent, tafluprost, may have similar efficacy as latanoprost but may be less effective compared to travoprost.[46-48] In one study, there was no difference in the reduction in IOP from baseline between tafluprost and travoprost following six weeks of treatment (difference, 0.170 mm Hg; 95% CI -1.268 to 1.608; *P*=0.811).[46] 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); adverse events were similar between the treatment groups.[48] In a randomized, double-blind trial (N=533), tafluprost demonstrated noninferiority to latanoprost treatment after 24 months, and no differences in the incidence of adverse events were reported between the two treatments (*P*<0.05).[47] In a noninterventional study by Erb and colleagues, patients with an inadequate response with prior therapies experienced a significantly lower IOP after switching to tafluprost treatment for 6 to 12 weeks compared to baseline (19.5±4.4 vs 16.4±2.9 mm Hg; *P*<0.001).[44] Results from a similar study showed a significantly lower incidence of eye irritation/burning, tearing, itching, dry eye sensation and conjunctival hyperaemia when switched to tafluprost therapy after experiencing ocular intolerance to latanoprost (*P*<0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mm Hg; *P*=0.049).[45]

In a study comparing bimatoprost 0.03% and travoprost, the mean reduction in IOP was significantly greater with bimatoprost 0.03% at 9 AM (P<0.014), but not at 1 PM (P=0.213) and 4 PM (P≥0.207).[18] A meta-analysis found that changes 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). In this same meta-analysis, bimatoprost 0.03% demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no significant differences observed between latanoprost and travoprost at any time point.[26] In a study evaluating bimatoprost 0.03%, latanoprost and travoprost, the mean changes in IOP were comparable between all treatment groups at week 12 (P=0.128), however, latanoprost was associated with fewer adverse events compared to bimatoprost (P<0.001).[24] In a meta-analysis of IOP measurements at peak and trough, bimatoprost 0.03% showed greater reductions in peak IOP than latanoprost; however, reductions were larger with latanoprost at the trough measurement.[31] The results from a similar meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (P=0.8) or latanoprost and travoprost (P=0.07).[30] It is important to note that absolute reductions in IOP between agents, although consistent, were sometimes small and the clinical significance of these differences is unknown.

As a class, the ophthalmic prostaglandin analogues have consistently showed greater efficacy in reducing IOP compared to ophthalmic β adrenergic antagonists, the only other class recommended as first-line therapy.[9-10] In a randomized controlled study, treatment with latanoprost was associated with greater reductions in IOP compared to treatment with betaxolol, carteolol, and nipradilol (P<0.05).[42] In addition, a meta-analysis of 11 randomized control trials showed significant reductions in IOP with latanoprost compared to ophthalmic timolol (P<0.001).[33]

The ophthalmic prostaglandin analogues have consistently shown greater efficacy in reducing IOP compared to agents in other classes used as monotherapy.[24,33,38] The only agent that showed similar reductions compared to ophthalmic prostaglandin analogues as monotherapy was brimonidine, which showed similar reductions in IOP compared to latanoprost (P=0.30), but was associated with a higher incidence of adverse events (31 vs 21%; P=0.0005).[39] The results from a meta-analysis by Cheng et al showed that ophthalmic brimonidine had the largest reduction in IOP at peak compared to all other glaucoma agents, however, brimonidine was also found to have the smallest reduction in IOP at the trough timepoint.[31]

The ophthalmic prostaglandins analogues have consistently demonstrated comparable or greater efficacy when compared to combination therapy.[28-29,34-37,40-41] Bimatoprost 0.03% showed greater reductions in IOP compared to dorzolamide/timolol in a six-week crossover study (P=0.03).[28] In a meta-analysis of 14 trials, latanoprost and dorzolamide/timolol had similar reductions in IOP at six months (P=0.28).[37] An open-label study comparing latanoprost to dual therapy with an ophthalmic β adrenergic antagonists showed similar reductions in IOP between both treatment groups (P=0.122).[40]

A meta-analysis of 13 studies evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% (P<0.00001) and travoprost (P<0.0001).[51] Moreover, one study evaluating the effect of latanoprost 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).[52] One study evaluated the use of travoprost without the preservative benzalkonium chloride (BAK) found that it had a lower incidence of hyperemia compared to ophthalmic travoprost with BAK (P values not reported).[54] The results from a second study showed that travoprost without BAK was associated with lower Ocular Surface Disease Index scores compared to bimatoprost 0.03% (P<0.0001) 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[16] Bimatoprost 0.01% 1 drop in the affected eye(s) QD between 7 PM and 9 PM vs bimatoprost 0.0125% 1 drop in the affected eye(s) QD between 7 PM and 9 PM vs bimatoprost 0.03% 1 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 of 22 to 34 mm Hg or less in each eye and best-corrected visual acuity equivalent to a Snellen score of 20/100 or better 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 at least 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 noninferior in efficacy to bimatoprost 0.03% based on predetermined criteria (limit of the 95% confidence interval of the between-group 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%) for bimatoprost 0.01%, 7.0 mm Hg (-28%) with bimatoprost 0.0125% and 7.6 mm Hg (-30%) for bimatoprost 0.03% at the 8 AM, evaluation At 12 noon, the average IOP reduction was 5.8 mm Hg (-25%) for bimatoprost 0.01%, 5.6 mm Hg (-24%) for bimatoprost 0.0125% and 6.3 mm Hg (-27%) for bimatoprost 0.03%. At 4 PM, IOP was reduced by 5.2 mm Hg (-23%) in patients treated with bimatoprost 0.01% and 0.0125% and 5.6 mm Hg (25%) for bimatoprost 0.03%. Secondary: The difference between changes from baseline diurnal IOP between bimatoprost 0.01% and bimatoprost 0.03% across all visits was 0.43 mm Hg, demonstrating noninferiority (95% CI upper limit being 0.93 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The difference between bimatoprost 0.0125% and bimatoprost 0.03% was 0.56 mm Hg (95% CI upper limit of 1.06). 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[17] Bimatoprost 0.03% 1 drop in the affected eye(s) QPM vs latanoprost 0.005% 1 drop in the affected eye(s) QPM	MA of 13 RCT's Patients with glaucoma (>21 mm Hg without medication and a glaucomatous visual field, optic disc changes, or retinal fiber layer defects) or ocular	N=1,032 Up to 6 months	Primary: Percent reduction in IOP from baseline to endpoint Secondary: Proportion of patients reaching target IOP of ≤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 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hypertension (IOP >21 mm Hg without medication and a normal visual field, optic disc, and retinal nerve fiber layer), IOP between 22 and 38 mm Hg after washout			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; *P* value not reported) favoring bimatoprost. Secondary: At three months, a significantly higher proportion of patients treated with bimatoprost compared to latanoprost (50.0 vs 37.6%) reached the target IOP of ≤17 mm Hg (pooled risk difference, 12%; 95% CI, 4 to 21; *P*=0.004). The differences in percentage of 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%, respectively; pooled risk difference, 20%; 95% CI, 15 to 24; *P*<0.001). Rate 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[18] Bimatoprost 0.03% 1 drop in the affected eye(s) QD between 7 PM and 9 PM vs travoprost 0.004% 1 drop in the affected eye(s) QD between 7 PM and 9 PM	DB, MC, PG, PRO, RCT Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension, untreated IOP of ≥21 and ≤34 mm Hg	N=157 6 months	Primary: Mean change in IOP from baseline, proportion of patients reaching target IOP reduction Secondary: Physician's assessment of clinical success, adverse events	Primary: Mean changes in IOP with bimatoprost at 9 AM, 1 PM, and 4 PM were -7.1, -5.9, and -5.3 mm Hg, respectively. Mean changes 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 1 PM (*P*=0.213) or 4 PM (*P*≥0.207) at six months. A reduction in IOP of ≥20.0% was seen in 77.6% of bimatoprost-treated patients compared to 64.2% of travoprost-treated patients (*P*=0.065). A reduction in IOP of ≥25.0% was seen in 64.5% of bimatoprost patients compared to 39.5% of travoprost patients (*P*=0.002). A reduction in IOP of ≥30.0% was seen in 38.2% of bimatoprost patients compared to 28.4% of travoprost patients (*P*=0.194).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). Rates of ocular redness, ocular itching, and hyperemia were comparable between the bimatoprost and travoprost groups.
Macky et al[19] Bimatoprost 0.03% 1 drop in the affected eye(s) QD between 9 PM and 10 PM vs travoprost 0.004% 1 drop in the affected eye(s) QD between 9 PM and 10 PM	MC, PRO, RCT Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension and the untreated IOP in each eye was ≥21 and ≤35 mm Hg	N=72 6 months	Primary: Mean change in IOP from baseline to week two, month one, two, four and six Secondary: Adverse events, clinically successful treatment (continuing on treatment past six months based on efficacy and tolerability)	Primary: After six months, 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 the discontinuation of the medication in either group. The rate of clinical success was similar between treatment groups. In the bimatoprost group, 85.3% of patients were considered to be successful compared to 73.3% of travoprost-treated patients (*P*=0.456).
Kammer et al[20] Bimatoprost 0.03% 1 drop in the affected eye(s) QPM	MC, PG, SB, RCT Adults with	N=266 3 months	Primary: Mean IOP at each time point and mean	Primary: After switching treatment from latanoprost therapy, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs travoprost 0.004% 1 drop in the affected eye(s) QPM	glaucoma or ocular hypertension in each eye with inadequate IOP control after ≥30 days on latanoprost monotherapy and best-corrected visual acuity equivalent to a Snellen score of 20/100 or better in each eye		diurnal IOP Secondary: Ocular signs on biomicroscopy, adverse events and visual acuity	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 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 hyperaemia and punctuate keratitis were the only findings with >one-grade increases in severity reported in at least 4% of patients in either treatment group. At month-three, the percentages of patients with a one-grade, two-grade or three-grade increase in the severity of conjunctival hyperaemia from baseline, 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 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 hyperaemia 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.
Sawada et al[21] Latanoprost 0.005% 1 drop in the affected eye(s) QD at 9 PM	OL, PRO, RCT, XO Patients with open-angle	N=42 XO at 12 weeks, 24 weeks total	Primary: Change from baseline in IOP, CCT and adverse events	Primary: There was a significant difference in diurnal IOP from baseline with latanoprost and travoprost (*P*<0.001). The differences in the IOPs for the individual times points were not significant between the two treatments (10 AM, *P*=1.000; 12 noon, *P*=1.000; 4 PM, *P*=1.000).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs travoprost 0.004% 1 drop in the affected eye(s) QD at 9 PM	glaucoma		Secondary: Not reported	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 to 528.42 µm at six months (*P*=0.0041, 0.0048, and 0.0011 respectively). There was a significant difference in CCT at six months in eyes initially treated with latanoprost compared to baseline CCT (*P*=0.0473). Additionally, a significant difference between the CCT at three months and six months in eyes of patients started with latanoprost (*P*=0.0305). 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.
Enoki et al[22] Latanoprost 0.005% 1 drop in the affected eye(s) QD vs unoprostone* 0.12% 1 drop in the affected eye(s) BID	OL, OS, PRO Patients previously treated with unoprostone for ≥3 months to treat normal-tension, open-angle glaucoma, with glaucomatous changes and defects	N=34 3 months	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, adverse events	Primary: Changes in IOP with latanoprost showed significant reductions compared to unoprostone of 1.8, 2.9, and 2.3 mm Hg at months one, two, and three, respectively (*P*<0.001). Secondary: Patients with an IOP of >12 mm Hg during unoprostone treatment had significant reductions in IOP of 2.1, 3.2, and 2.9 mm Hg after treatment with latanoprost for months one, two and three months, respectively (*P*<0.0001). Patients with an IOP of ≤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).

<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>One patient reported ocular foreign sensation with latanoprost. No serious adverse events were observed.</td></tr>
<tr><td>Jampel et al[23]

Latanoprost 0.005% 1 drop in the affected eye(s) QPM

vs

unoprostone* 0.12% 1 drop in the affected eye(s) BID</td><td>DB, MC, PG, PRO, RCT

Patients ≥18 years of age, current or previous treatment for intraocular control, visual acuity of ≥20/80</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 between groups in IOP from baseline, proportion of patients achieving specific IOP levels and adverse events</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 (8 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 (8 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><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:
Overall mean percent reduction in IOP was significantly greater with latanoprost compared to unoprostone (28 vs 15%; P<0.001).

IOP reductions of >40% and >30% were seen 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 seen in either group.</td></tr>
<tr><td>Parrish et al[24]

Bimatoprost 0.03% 1 drop in the affected eye(s) QD at 8 PM</td><td>DB, MC, PG, RCT

Patients ≥18 years of age with primary open-</td><td>N=410

12 weeks</td><td>Primary:
Mean change in IOP at 8 AM at 12 weeks

Secondary:</td><td>Primary:
At week 12, the mean changes 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).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs latanoprost 0.005% 1 drop in the affected eye(s) QD at 8 PM vs travoprost 0.004% 1 drop in the affected eye(s) QD at 8 PM	angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular hypertension (≥21 mm Hg); current or previous therapy with topical ocular hypotensive agent; visual acuity of ≥20/200		Mean change in diurnal IOP and adverse events	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 with 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. The difference in hyperemia incidence between the bimatoprost group and latanoprost group was statistically significant (*P*=0.001).
Faridi et al[25] Bimatoprost 0.03% 1 drop in the affected eye(s) QPM vs latanoprost 0.005% 1 drop in the affected eye(s) QPM vs travoprost 0.004% 1 drop in the affected eye(s) QPM	PRO, RCT, SB Newly diagnosed patients with ocular hypertension or open-angle glaucoma, including normal tension glaucoma	N=122 6 months	Primary: Change in IOP from baseline after two and six months, tolerance profiles Secondary: Not reported	Primary: After two months of treatment, patients treated with bimatoprost experienced a greater reduction in IOP compared to latanoprost and travoprost (9.45 vs 6.17 and 7.36 mm Hg, respectively; *P*=0.013). At six months, bimatoprost had a greater reduction in 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). Side effect profiles were similar between the groups (*P*=0.60 and *P*=0.34) at the two-month and six-month follow-up visits, respectively.
Aptel et al[26] Bimatoprost 0.03% 1 drop	MA of 8 RCT's Patients with	N=1,610 3 months	Primary: Mean IOP change from	Primary: The difference in absolute IOP reduction from baseline was significantly greater with bimatoprost at all time points compared with latanoprost (8

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in the affected eye(s) QPM between 6 PM and 10 PM vs latanoprost 0.005% 1 drop in the affected eye(s) QPM between 6 PM and 10 PM vs travoprost 0.004% 1 drop in the affected eye(s) QPM between 6 PM and 10 PM	open-angle glaucoma or ocular hypertension; prostaglandin analogue monotherapy; no systemic/ocular medications or laser/surgery that could affect IOP in past three months		baseline at 8 AM, 12 noon, 4 PM and 8 PM Secondary: Conjunctival hyperemia	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. A statistically significant difference was not seen between bimatoprost and travoprost at 4 PM (*P*=0.190) and 8 PM *(P*=0.070). Reductions in IOP were comparable between latanoprost and travoprost for all time points (8 AM; *P*=0.100; 12 noon; *P*=0.380; 4 PM; *P*=0.820; 8 PM; *P*=0.670). Secondary: The incidence of self-reported hyperemia was significantly higher with bimatoprost compared to latanoprost (0.48 vs 0.26%; RR, 1.70; 95% CI, 1.44 to 2.02; *P*<0.001). The incidence of self-reported hyperemia was significantly higher with bimatoprost compared to 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[27] Bimatoprost 0.03% 1 drop in the affected eye(s) QPM vs	MA of 9 RCT's Patients with open-angle glaucoma or ocular hypertension	N=1,318 Duration varied from 2 weeks to 12 months; mean time of follow	Primary: Average IOP at the end of follow up period Secondary: Adjusted	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:

<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% 1 drop in the affected eye(s) QPM

vs

travoprost 0.004% 1 drop in the affected eye(s) QPM</td><td></td><td>up was 4.3 months</td><td>treatment effect on IOP at the end of follow up period, adjusting for baseline and duration of follow-up</td><td>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).</td></tr>
<tr><td>Sharpe et al[28]

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 with 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 response to latanoprost (IOP of ≥21 mm Hg)</td><td>N=30

XO at 6 weeks, 12 weeks total</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 from baseline, visual acuity and adverse events</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><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</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></td><td></td><td></td><td>(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[29]

Timolol/dorzolamide 0.5%/2.0% 1 drop in the affected eye(s) BID

vs

bimatoprost 0.03% 1 drop in the affected eye(s) QD at 8 PM</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 timolol/dorzolamide group compared to 6.2±1.8 mm Hg in the bimatoprost group (P=0.48).

Secondary:
No statistically significant differences were found with regard to the occurrence of burning and/or stinging, bitter taste, dry eye, eyelid eczema, or breathlessness (P=>0.05 for all).

Conjunctival hyperemia occurred in significantly more patients in the timolol/dorzolamide group than in the bimatoprost group (P=0.02).</td></tr>
<tr><td>Holstrom et al[14]

Bimatoprost

vs

latanoprost

vs

travoprost

vs

timolol

Dosing not specified for any of the regimens.</td><td>SR of 42 RCT’s

Patients ≥18 year of age with primary open-angle glaucoma</td><td>N=9,295

Duration not specified</td><td>Primary:
IOP reduction in the morning, additional IOP reduction compared to timolol, percent of patients meeting IOP thresholds

Secondary:
Not reported</td><td>Primary:
As a class, prostaglandin monotherapy was more efficacious than timolol monotherapy in decreasing IOP. At one, three, and six months, prostaglandins decreased IOP by 27.2, 28.8 and 28.6%, compared to 21.2, 22.2 and 22.2%, respectively, with timolol (P value not reported).

Additional reductions in IOP of 1.55, 1.47 and 0.44 mm Hg were reported with bimatoprost, latanoprost and travoprost, respectively, compared to timolol after six months of treatment (P value not reported).

An analysis of the percentage of patients reaching targeted IOPs showed 7 to 29% more of the bimatoprost patients achieved a targeted intraocular than latanoprost patients. No travoprost data was reported.

Percent of Patients Reaching IOP Target (maximum three months)
<table><tr><td></td><td colspan="8">Target IOP (mm Hg)</td></tr><tr><td></td><td>≤13</td><td>≤14</td><td>≤15</td><td>≤16</td><td>≤17</td><td>≤18</td><td>≤19</td><td>≤20</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></td><td></td><td></td><td>
<table>
<tr><td>Bimatoprost</td><td>16%</td><td>26%</td><td>39%</td><td>52%</td><td>62%</td><td>72%</td><td>76%</td><td>85%</td></tr>
<tr><td>Bimatoprost and brimonidine</td><td>-</td><td>-</td><td>8%</td><td>31%</td><td>39%</td><td>69%</td><td>76%</td><td>85%</td></tr>
<tr><td>Latanoprost</td><td>9%</td><td>17%</td><td>21%</td><td>35%</td><td>48%</td><td>55%</td><td>61%</td><td>72%</td></tr>
<tr><td>Latanoprost and timolol</td><td>-</td><td>-</td><td>-</td><td>26%</td><td>38%</td><td>42%</td><td>69%</td><td>82%</td></tr>
<tr><td>Travoprost</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Timolol</td><td>9%</td><td>15%</td><td>21%</td><td>30%</td><td>40%</td><td>53%</td><td>57%</td><td>65%</td></tr>
</table>

Six head-to-head trials evaluating bimatoprost vs latanoprost showed bimatoprost to be more efficacious in lowering IOP. Two head-to-head trials evaluating bimatoprost vs travoprost showed bimatoprost to be more efficacious in lowering IOP. Two head-to-head trials comparing latanoprost and travoprost showed comparable reductions in IOP.

Discontinuation due to adverse events was reported in 4.3, 4.5 and 2.0% of bimatoprost, latanoprost and travoprost patients, respectively.

Secondary:
Not reported</td></tr>
<tr><td>Li et al[30]

Bimatoprost 0.03%

vs

latanoprost 0.005%

vs

travoprost 0.004%

vs</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 in lowering IOP compared to timolol (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 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 compared to travoprost 0.0015% (-0.32 mm Hg; 95% CI, -0.62 to -0.02; P=0.04).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
travoprost 0.0015%† vs unoprostone 0.12%* vs timolol 0.05% Dosing not specified for any of the regimens.				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 compared to 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[31] 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 vs	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	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 (relative reduction, 21%; 95% CI, 16 to 25; absolute reduction, 3.4 mm Hg; 95% CI, 2.7 to 4.2), latanoprost (relative reduction, 20%; 95% CI, 17 to 24; absolute reduction, 3.3 mm Hg; 95% CI, 2.7 to 3.8), timolol (relative reduction, 15%; 95% CI, 12 to 18; absolute reduction, 2.4 mm Hg; 95% CI, 2.0 to 2.8), dorzolamide (relative reduction, 14%; 95% CI, 8 to 19; absolute reduction, 2.1 mm Hg; 95% CI, 1.3 to 3.0), brinzolamide (relative reduction, 13.0%; 95% CI, 6.0 to 20.0; absolute reduction, 1.9 mm Hg; 95% CI, 0.9 to 2.9), and betaxolol (relative reduction, 12%; (95% CI, 1.0 to 23.0; absolute reduction, 2.0 mm Hg; 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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	glaucomatous visual field defects and corresponding optic disc damage; and the absence of a secondary cause for IOP elevation			reduction, 3.3 mm Hg; 95% CI, 2.9 to 3.6); followed by bimatoprost (relative reduction, 18.0%; 95% CI, 14.0 to 22.0; absolute reduction, 2.9 mm Hg; 95% CI, 2.2 to 3.5), timolol (relative reduction, 18.0% (95% CI, 8.0 to 27.0; absolute reduction, 3.0 mm Hg; 95% CI, 1.7 to 4.3), dorzolamide (relative reduction, 12.0%; 95% CI, -7.0 to 31.0; absolute reduction, 3.0 mm Hg; 95% CI, 1.7 to 4.3), and brimonidine (relative reduction, 11.0%; 95% CI, 7.0 to 14.0; absolute reduction, 1.7 mm Hg; 95% CI, 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 et al[15] 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, N=6,841 (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 highest mean reduction of IOP seen at trough from baseline occurred with 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).

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				Secondary: Not reported
Varma et al[32] Latanoprost 0.005% 1 drop in the affected eye(s) QPM vs	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 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-treated patients compared to latanoprost (6 vs 11%; *P*=0.026). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
timolol 0.5% 1 drop in the affected eye(s) BID				Not reported
Zhang et al[33] 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: Percent 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 treatments significantly lowered IOP compared to baseline values. 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 compared to 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 with zero 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[34] Timolol/dorzolamide 0.5%/2.0% 1 drop into affected eye(s) BID and latanoprost 0.005% 1 drop into affected eye(s) QD vs timolol/dorzolamide 0.5%/2.0% 1 drop into affected eye(s) BID	MC, OL, PRO Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension, previously treated with latanoprost monotherapy for ≥4 weeks with	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 treatment groups reported statistically significant changes in mean absolute and percent reductions in IOP at six and 12 weeks when compared to baseline (P<0.001). The changes in IOP between the groups at weeks six and 12 were not found to be statistically significant (P value not reported). Secondary: Therapeutic response rates of >20% occurred after 12 weeks of treatment in 66.4% of the patients in the timolol/dorzolamide with latanoprost group and 52.9% of the patients in the timolol/dorzolamide group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	continued IOP >21 mm Hg or <15% reduction in IOP, deterioration of the visual fields regardless of IOP target			The most frequent adverse events reported for both groups were eye irritation and bad taste in the mouth (12.0 and 4.3%), respectively.
Fechtner et al[35] Dorzolamide/timolol 2%/0.5% 1 drop into both eye(s) QD at 8 AM and 8 PM vs latanoprost 0.005% 1 drop into both eyes QD at 8 PM and placebo at 8 AM	2 DB, MC, PG, RCT Patients ≥18 years of age 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 the dorzolamide/timolol fixed dose combination than latanoprost (95% 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 fixed dose combination than latanoprost (95% CI, -1.31 to 0.16). Secondary: Study 1: Adverse events that occurred in both groups were mild to moderate and localized to the eye. 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 fixed dose combination 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 event in the study was ocular stinging (10 vs 2%) which occurred significantly more in the dorzolamide/timolol fixed dose combination group compared to the latanoprost group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Taste perversion occurred in only 2% of patient in the dorzolamide/timolol fixed dose combination group and was not present in the latanoprost group; however, the results were not significant (*P* value not reported).
Konstas et al[36] Latanoprost 0.005% 1 drop in the affected eye(s) QPM and placebo 1 drop in the affected eye(s) QD at 8 PM and placebo at 8 PM vs dorzolamide/timolol 2%/0.5% 1 drop in the affected eye(s) at 8 AM and 8 PM	DB, DD, MC, PRO, RCT, XO Patients >39 years of age, normal-appearing angles, either ocular hypertension or primary open-angle glaucoma, and IOP ≥24 mm Hg after six week washout period	N=53 XO at 6 months, 12 months total	Primary: Mean 24-hour IOP Secondary: Mean 24-hour IOP at month six, comparison between treatments at month two, change in individual treatment pressure from month two to six and adverse events	Primary: Both treatments showed reductions in IOP compared to baseline at six months on the 24-hour curve (*P*=0.03). Additionally, all patients had a >15% reduction in IOP during latanoprost treatment. Mean 24-hour IOPs were comparable between the latanoprost and dorzolamide/timolol groups (18.3±1.9 vs 18.1±1.9 mm Hg, respectively; *P*=0.3), as were the maximum (*P*=0.8), minimum (*P*=0.5) and range (*P*=0.4) IOPs. Secondary: After two months, the dorzolamide/timolol group demonstrated a significant decrease in mean 24-hour IOP compared to the latanoprost group (18.0±1.8 vs 18.6±1.8 mm Hg; *P*=0.0002). From month two to six, the latanoprost group showed a significant reduction in IOP (0.4±1.0 mm Hg; *P*=0.01). Changes in IOP from months two to six were not significant in the dorzolamide/timolol group (*P*=0.8). Dorzolamide/timolol was associated with higher rates of burning and stinging (*P*<0.001) and bitter taste (*P*=0.002) compared to the latanoprost group. Latanoprost was associated with significantly higher rates of hypertrichosis (*P*=0.02), headache (*P*=0.04) and ocular itching (*P*=0.004).
Cheng et al[37] Latanoprost 0.005% 1	MA of 14 RCT's Patients with	N=2,149 Duration	Primary: Reduction from baseline in	Primary: Changes in mean reduction in IOP were comparable at one, two, three, and six months between latanoprost and dorzolamide/timolol therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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)	glaucoma (excluding normal tension glaucoma) or ocular hypertension	varied from 4 weeks to 6 months	diurnal mean IOP Secondary: Reduction from baseline to endpoint in IOP at 10 AM within a range of ±1 hour	At one month, the mean reduction in IOP was 29.59% with latanoprost compared to 32.81% with dorzolamide/timolol therapy (*P*=0.08). At two months, the mean reduction in IOP was 28.38% with latanoprost compared to 30.26% with dorzolamide/timolol therapy (*P*=0.19). At three months, the mean reduction in IOP was 24.83% with latanoprost compared to 24.26% with the dorzolamide/timolol therapy (*P*=0.71). At six months, the mean reduction in IOP was 30.62% with latanoprost compared to 35.76% with the dorzolamide/timolol therapy (*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 therapy. At one month, the mean reduction in IOP at 10 AM was 26.86% with latanoprost compared to 29.33% with dorzolamide/timolol therapy (*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 therapy (*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 therapy (*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 therapy (*P*=0.25). Rates of ocular adverse events did not differ significantly between latanoprost and dorzolamide/timolol therapy (pooled RR, 0.96; 95% CI, 0.21 to 4.46; *P*=0.96). Latanoprost was associated with higher rates of conjunctival hyperemia compared with dorzolamide/timolol therapy (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 with dorzolamide/timolol therapy (2.7 vs 0.0%; RR, 8.11; 95% CI, 1.47 to 44.75; *P*=0.02). Dorzolamide/timolol therapy was associated with higher discontinuation 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 therapy 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[38] 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	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 mm Hg (95% CI, -5.2 to -4.6) at trough and peak, respectively. The relative changes in IOP were -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 gave an absolute pooled mean change from baseline of -6.0 mm Hg (95% CI, -6.8 to -5.2) and relative change of -26.9% (95% CI, -32.7 to -21.1). The fixed combination of latanoprost and timolol gave an absolute pooled mean change from baseline of -3.0 mm Hg (95% CI, -3.8 to -2.2) and relative change of -13.4% (95% CI, -16.0 to -10.8). Secondary: Not reported
Hodge et al[39] Latanoprost vs	SR of 8 RCT's Patients ≥18 years of age with raised IOP,	N=1,178 Minimum duration of 3 months	Primary: Difference in reduction of IOP Secondary:	Primary: Latanoprost did not show a significant reduction in mean IOP compared to brimonidine (WMD, -1.04; 95% CI, -3.01 to 0.93; *P*=0.30). Latanoprost showed a significant reduction in mean IOP compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
brimonidine vs dorzolamide Dosing not specified for any of the regimens.	treatment naïve or washout period prior to treatment		Adverse events and withdrawals due to adverse effects	dorzolamide (WMD, -2.64; 95% CI, -3.25 to -2.04; *P*<0.00001). Secondary: Rates of ocular adverse events were higher with brimonidine compared to latanoprost (31 vs 21%; RR, 0.66; *P*=0.0005). Rates of discontinuation due to adverse events, ocular hyperemia and serious adverse events were comparable between latanoprost and brimonidine therapy. Rates of discontinuation due to adverse events, ocular adverse events, ocular hyperemia and serious adverse events were comparable between latanoprost and dorzolamide therapy.
Pillunat et al[40] Latanoprost 0.005% 1 drop in the affected eye(s) QD at 10 PM vs dual ocular hypotensive therapy including a β adrenergic antagonist Dosing not specified for any of the dual therapy regimens.	OL, PG, PRO, RCT Patients ≥18 years of age with an IOP of ≤21 mm Hg on current therapy; mild to moderate primary open-angle glaucoma, pigmentary glaucoma, or capsular glaucoma	N=466 6 months	Primary: Diurnal IOP change, successfully controlled patients (≤22 mm Hg and ≤15% decrease from baseline) Secondary: Clinical success rates (investigator's determination that a change in therapy from baseline assignment was not needed) and adverse events	Primary: Diurnal IOP slightly decreased, but did not differ significantly from baseline, after six months in patients randomized to latanoprost (-0.26±0.18 mm Hg; *P*=0.153). Diurnal IOP slightly decreased, but did not differ significantly from baseline, after six months in patients who remained on dual therapy (-0.37±0.26 mm Hg; *P*=0.138). The difference in mean diurnal pressure, 0.11 mm Hg, between the latanoprost and dual therapy group did not differ significantly (95% CI, -0.59 to 0.36; *P*=0.641). IOP reduction success rates were comparable in the latanoprost and dual therapy groups (83 vs 89%, respectively; *P*=0.122). Secondary: Clinical success rates were comparable in the latanoprost and dual therapy groups (97 vs 99%, respectively; *P*=0.161). The incidence of adverse events was 23% in both treatment groups. Visual field deterioration occurred in more patients receiving dual

<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>therapy than latanoprost therapy (9 vs 2%; P=0.002).</td></tr>
<tr><td>Bayer et al[41]

Latanoprost 0.005% 1 drop in the affected eye(s) QPM

vs

historical control (betaxolol, brimonidine, carteolol, clonidine, dipivefrin, dorzolamide, dorzolamide and clonidine, dorzolamide and timolol, dorzolamide/timolol, levobunolol, metipranolol, pilocarpine, pilocarpine/metipranolol, pilocarpine/timolol, or timolol)

Dosing not specified for any of the historical control regimens.</td><td>MC, OL, OS, PRO

Patients with open-angle, exfoliative or chronic angle-closure glaucoma treated ≥3 months with previous glaucoma therapy which physicians had already decided to switch to latanoprost therapy due to inadequate response, adverse events, poor adherence or ease of dosing</td><td>N=1,571

2 years</td><td>Primary:
Change in IOP

Secondary:
Adverse events and percent of patients discontinuing latanoprost</td><td>Primary:
The IOP showed a decrease of 17.4% across all treatment groups after switching to latanoprost (21.3±4.1 vs 17.6±3.2 mm Hg; P≤0.001). Statistical differences were seen across each treatment subgroup.

IOPs After Switching to Latanoprost (mm Hg±SD)
<table><tr><th>Previous therapy</th><th>N</th><th>Follow up</th><th>Change From Baseline</th><th>P value</th></tr><tr><td>Betaxolol</td><td>40</td><td>17.1±3.6</td><td>-4.5</td><td><0.001</td></tr><tr><td>Brimonidine</td><td>125</td><td>18.3±3.3</td><td>-3.2</td><td><0.001</td></tr><tr><td>Carteolol</td><td>33</td><td>18.0±2.9</td><td>-4.3</td><td><0.001</td></tr><tr><td>Clonidine</td><td>154</td><td>17.9±2.7</td><td>-4.0</td><td><0.001</td></tr><tr><td>Dipivefrin</td><td>27</td><td>16.2±2.3</td><td>-5.1</td><td><0.001</td></tr><tr><td>Dorzolamide</td><td>309</td><td>17.7±3.6</td><td>-3.6</td><td><0.001</td></tr><tr><td>Dorzolamide and clonidine</td><td>21</td><td>17.1±2.7</td><td>-4.1</td><td><0.001</td></tr><tr><td>Dorzolamide and timolol</td><td>50</td><td>17.3±3.4</td><td>-4.6</td><td><0.001</td></tr><tr><td>Dorzolamide/timolol</td><td>32</td><td>17.0±2.9</td><td>-4.5</td><td><0.001</td></tr><tr><td>Levobunolol</td><td>79</td><td>17.4±2.7</td><td>-3.5</td><td><0.001</td></tr><tr><td>Metipranolol</td><td>60</td><td>17.2±2.7</td><td>-3.3</td><td><0.001</td></tr><tr><td>Pilocarpine</td><td>83</td><td>17.8±3.3</td><td>-2.8</td><td><0.001</td></tr><tr><td>Pilocarpine/ metipranolol</td><td>48</td><td>19.1±4.5</td><td>-1.7</td><td>0.0028</td></tr><tr><td>Pilocarpine/timolol</td><td>48</td><td>17.9±3.0</td><td>-3.7</td><td><0.001</td></tr><tr><td>Timolol</td><td>462</td><td>17.4±3.1</td><td>-3.7</td><td><0.001</td></tr></table>
Secondary:
The most common adverse event associated with latanoprost, irritation,</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was reported in 1.6% of patients. Ocular adverse events seen in <1% of patients included inflammation, uncontrolled IOP, conjunctival hyperemia and visual complaint. A total of 13.2% of patients discontinued therapy with latanoprost during the trial. The most common reasons were loss to follow-up (31.4%) and undesirable adverse events (22.2%).
Ikeda et al[42] Latanoprost QD vs betaxolol BID vs carteolol BID vs nipradilol BID Dosing not specified for any of the regimens.	PRO, RCT, XO 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 of ≤10%)	Primary: At three months, mean IOPs in the betaxolol, carteolol and nipradilol groups were 12.9, 12.4 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 mm Hg, respectively, all of which were statistical significant (*P*<0.05). Secondary: At three months, the percent reductions in IOP with betaxolol, carteolol, and nipradilol were 10.8, 10.4 and 9.5%, respectively. After switching to latanoprost for three months, the percent reductions in IOP were 19.4, 24.1 and 22.9%, respectively. Reductions with latanoprost compared to the betaxolol, carteolol, and nipradilol were all statistically significant (*P*<0.05). β adrenergic antagonists were associated with a significantly higher portion of non-responders compared to latanoprost (53.5 vs 20.9%; *P*=0.0257).
Hommer et al[43] Tafluprost 0.0015% 1 drop in the affected eye(s) QD vs historical control (β adrenergic antagonist, CAI and PGA, alpha$_2$-	MC, OL, Patients with glaucoma or ocular hypertension who required a change of medication, an add-on therapy	N=544 12 weeks	Primary: Change from baseline in IOP and adverse events Secondary: Not reported	Primary: After four to six weeks of treatment, patients switched to tafluprost experienced significantly greater reduction in IOP compared to baseline (15.7±4.1 vs 19.4±5.0 mm Hg; *P*<0.001). Tafluprost significantly lowered IOP compared to baseline IOP at four to six weeks among all prior treatment groups (*P*<0.001 for all). This includes patients switched from monotherapy with a β adrenergic antagonist (15.5 vs 21.1 mm Hg), PGA (15.0 vs 16.2 mm Hg) or a CAI (14.8 vs 19.2 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
adrenergic agonists, miotics, fixed combination therapy) Dosing not specified for any of the historical control regimens.	or who were naive to medical treatment			At 12 weeks, IOP continued to be lower with tafluprost treatment compared to baseline values (15.3±3.5 vs 19.4±5.0 mm Hg; *P*<0.001). This includes patients switched from monotherapy with a β adrenergic antagonist (15.5 vs 21.1 mm Hg), PGA (14.8 vs 16.2 mm Hg) or a CAI (15.0 vs 19.2 mm Hg). There was no difference in IOP between the four to six week period and 12 weeks for the treatment naïve patients. After 12 weeks of treatment, patients achieved an IOP reduction of 25.6, 21.9 and 8.7% when switching from β adrenergic antagonist, CAI and PGA, respectively. Less than 10% of patients reported adverse events. Forty seven patients (8.6%) terminated treatment during the 12 week follow-up period. The major reason for discontinuation was the lack of efficacy which was reported for 17 patients (3.1%), followed by local intolerance (14 patients; 2.6%), systemic side effects (four patients; 0.7%) and allergy (two patients; 0.4%).
Erb et al[44] Tafluprost 0.0015% 1 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 investigators determined to require 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 6 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 therapy after 6 to 12 weeks of treatment. Tafluprost was effective at lowering IOP across all prior monotherapy-subgroups (*P*<0.001 for all): 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). After 6 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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[45] Tafluprost 0.0015% 1 drop in the affected eye(s) QD vs historical control (latanoprost 0.005%) Dosing not specified for the historical control regimens.	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 exhibiting ≥2 ocular symptoms, or one symptom and one sign of ocular surface irritation/ inflammation	N=158 12 weeks	Primary: Change from baseline in IOP, proportion of patients reporting Irritation/burning/ stinging, foreign body sensation, tearing, itching, dry eye sensation, tBUT, corneal fluorescein staining, conjunctival fluorescein staining, blepharitis, conjunctival hyperaemia, tear secretion/ Schirmer's test Secondary: Not reported	Primary: Throughout the 12-week treatment period, 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 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 hyperaemia (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[46]	AC, DB, MC,	N=38	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tafluprost 0.0015% 1 drop in the affected eye(s) QD at 8PM vs latanoprost 0.005% 1 drop in the affected eye(s) QD at 8PM	PG, RCT Patients ≥18 years of age with primary open-angle glaucoma, exfoliation glaucoma, or ocular hypertension with an IOP of 22 to 34 mm Hg in at least one eye	6 weeks	Reduction in IOP and duration of action by day 42 and 43 Secondary: IOP values at 8 AM on days seven, 21 and 42 and proportion of patients reaching prespecified IOP reductions of ≥15%, ≥20%, ≥25% and ≥30%, overall adverse events, best-corrected visual acuity, conjunctival hyperemia, biomicroscopy, fundus examination, ocular symptoms, overall drop discomfort, blood pressure and heart rate	By day 42, the mean diurnal values for tafluprost and latanoprost, respectively, 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). 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 and latanoprost on days 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 [-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 of ≥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 reported in the tafluprost treatment group compared to 23 events reported in the latanoprost group. Three adverse events were considered severe, all of which occurred in the tafluprost group (two photophobias and one report of 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, and other) were comparable between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 treatment group.
Uusitalo et al[47] Tafluprost 0.0015% 1 drop in the affected eye(s) QD at 8PM vs latanoprost 0.005% 1 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, an untreated IOP of 22 to 34 mm Hg in at least one eye and a Snellen equivalent of 20/80 or better in each eye	N=533 104 weeks	Primary: Change from baseline in diurnal IOP, adverse events, ocular safety (best-corrected visual acuity), conjunctival redness, biomicroscopy, ophthalmoscopic-al evaluation, visual field test, iris color/ eyelash/lid photographs), overall drop discomfort, systemic (BP and HR) and laboratory safety variables Secondary: Not reported	Primary: After 24 months of treatment, the mean decrease in IOP from baseline in the tafluprost group was 7.1 mm Hg (-29.1%) compared to 7.7 mm Hg (-32.2%) in the latanoprost group. The upper limit of the 95% CI was 1.38, within the noninferiority limit of 1.5 mm Hg. Over 24 months, at least one adverse event was reported by 66.7% patients in the tafluprost group compared to 61.4% 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 hyperaemia (5.3 vs 2.7%). None of the differences in adverse events 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 treatment groups. A change from baseline of >0.2 LogMAR scores 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 treatment groups. Amongst patients treatment naïve to prostaglandins, there was a higher incidence of severe iris pigmentation in the latanoprost treatment group, however, the difference between groups after 24 months was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not statistically significant (*P*=0.848). The overall incidence of drop-discomfort was low in both treatment 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
Schnober et al[48] Tafluprost 0.0015% 1 drop in the affected eye(s) QD at 8 PM vs travoprost 0.004% 1 drop in the affected eye(s) QD at 8 PM	AC, DB, RCT, XO Patients ≥21 years 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 at the	N=51 XO at week 6, 12 weeks total	Primary: Mean IOP at 8 PM Secondary: Solicited symptom survey questions, hyperemia, and visual acuity	Primary: The mean reduction in IOP at 8 PM after six weeks of treatment was greater with travoprost treatment compared to tafluprost (7.2 vs 6.6 mm Hg; *P*=0.01). Patients 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 the 8 AM (*P*=0.06) and 2 PM (*P*=0.09) evaluation points. Secondary: There were no differences between tafluprost and travoprost treatment in regard to individual symptom scores (*P*>0.05 for all) Investigator-observed hyperemia was 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 with either travoprost or tafluprost treatment (*P*=0.49). No difference in patient tolerability was reported between the two treatment groups (*P*=0.18)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline visit and a best-corrected visual acuity of at least 20/200 in both eyes			
Chabi et al[49] Tafluprost 0.0015% 1 drop in the affected eye(s) QD vs timolol 0.5% 1 drop in the affected eye(s) BID	AC, DB, MC, NI, PG, RCT Patients ≥18 years of age with primary open-angle glaucoma, pigmentary glaucoma, capsular glaucoma/pseudoexfoliation, or ocular hypertension with a best-corrected visual acuity of 20/80 or better in each eye and a mean IOP ≤36 mm Hg in both eyes or ≥23 and ≤36 mm Hg in at least 1 eye and <5 mm Hg difference in mean IOP if discontinuing previous	N=643 12 weeks	Primary: Mean IOP change from baseline at all nine time points during the study (8 AM, 10 AM, and 4 PM at weeks two, six, and 12) Secondary: Proportion of patients with a ≥25% reduction in diurnal IOP and mean change from baseline in diurnal IOP at weeks two, six, and 12	Primary: Treatment with tafluprost was noninferior compared to timolol at all time points throughout the 12-week evaluation period. The reductions in IOP were apparent as early as week two of treatment at 8 AM (-0.4 mm Hg; 95% CI, -0.8 to 0.1), 10 AM (-0.7 mm Hg; 95% CI, -1.1 to -0.3) and 4 PM (-0.8 mm Hg; 95% CI, -1.3 to -0.4). At all time points, the upper limits of the confidence intervals for the difference between treatments in IOP lowering were less than the prespecified NI margin of 1.5 mm Hg. By week six, the change in IOP with talfuoprost continued to be noninferior to timolol at 8 AM, (0.1 mm Hg; 95% CI, -0.3 to 0.6), 10 AM, (-0.4 mm Hg; 95% CI, -0.9 to 0.0) and 4 PM (-0.8 mm Hg; 95% CI, -1.3 to -0.3). At week 12, tafluprost demonstrated similar IOP-reducing effect compared to timolol at 8 AM (0.0 mm Hg; 95% CI, -0.4 to 0.5), 10 AM (-0.4 mm Hg; 95% CI, -0.9 to 0.0) and 4PM (-0.6 mm Hg; 95% CI, -1.0 to -0.1). Secondary: At week two 56.7 and 50.5% of patients receiving tafluprost and timolol, respectively, experienced a ≥25% reduction in IOP from baseline (difference, 6.2%; 95% CI, -1.8 to 14.1). At week six 58.7 and 52.6% of patients receiving tafluprost and timolol, respectively, experienced a ≥25% reduction in IOP from baseline (difference, 6.2%; 95% CI, -1.7 to 14.0).

<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>treatments</td><td></td><td></td><td>At week 12, 59.7 and 55.4% of patients receiving tafluprost and timolol, respectively, experienced a ≥25% reduction in IOP from baseline (difference, 4.3%; 95% CI, -3.6 to 12.1).

There was a greater reduction in mean diurnal IOP from baseline in the tafluprost group compared to the timolol group at weeks two and six, but there was no difference between the treatments at week 12 (-0.3 mm Hg; 95% CI, -0.7 to 0.1).</td></tr>
<tr><td>Walters et al[50]

Timolol GFS 0.5% 1 drop into both eyes QD

vs

bimatoprost 0.03% 1 drop into both eyes QD

vs

latanoprost 0.005% 1 drop into both eyes QD</td><td>MC, RCT, SB

Adults with open-angle glaucoma or ocular hypertension requiring bilateral treatment, with an IOP in each eye between 22 and 34 mm Hg at baseline after washout of glaucoma medications, with asymmetry in IOP between eyes no more than 5 mm Hg, and a best corrected visual acuity of 20/100 or better in each eye</td><td>N=115

1 month</td><td>Primary:
Mean change in IOP from baseline

Secondary:
Percent of patients achieving target IOP level and adverse events</td><td>Primary:
<table><tr><th colspan="5">Mean IOP at 8AM</th></tr><tr><th>Day</th><th>Bimatoprost</th><th>Timolol GFS</th><th>Latanoprost</th><th>Among-Group P value*</th></tr><tr><td>0</td><td>24.1±0.4</td><td>24.4±0.4</td><td>23.6±0.3</td><td>0.335</td></tr><tr><td>14</td><td>16.0±0.5‡</td><td>18.6±0.5</td><td>17.0±0.5†</td><td>0.002</td></tr><tr><td>28</td><td>16.0±0.5‡</td><td>18.5±0.5</td><td>16.1±0.4†</td><td><0.001</td></tr><tr><td>29</td><td>14.6±0.6‡</td><td>17.5±0.6</td><td>16.0±0.6</td><td>0.002</td></tr></table>*None of the differences between the latanoprost and bimatoprost groups was statistically significant.
† P≤0.027 vs timolol GFS.
‡ P<0.001 vs timolol GFS.

All three treatment groups effectively reduced IOP from baseline and mean IOP was found to be significantly lower with bimatoprost when compared to timolol GFS at the 8 AM measurements at all follow-up visits and significantly lower with latanoprost when compared to timolol GFS at 8 AM on days 14 and 28 (P<0.001 and P<0.0027 respectively).

Secondary:
A higher percentage of patients in the bimatoprost and latanoprost groups achieved target IOP levels than patients in the timolol GFS group. This difference was statistically significant in the bimatoprost group at target pressures of ≤15, ≤16 and ≤17 mm Hg (P≤0.019) and in the latanoprost group at a target pressure of ≤17 mm Hg (P=0.022). More patients in the bimatoprost group achieved each target pressure from ≤13 to ≤18 mm Hg when compared to the latanoprost group;</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				however, this difference only reached statistical significance at a target pressure of ≤15 mm Hg (*P*≤0.038). The most common adverse event was conjunctival hyperemia and was reported in the bimatoprost, latanoprost and timolol GFS groups (39.5% vs 15.8% vs 2.6%; *P*=0.021 for bimatoprost vs latanoprost and *P*<0.001 for bimatoprost vs timolol). Eye pruritus occurred more frequently in the bimatoprost group followed by the latanoprost group and no reports in the timolol GFS group (13.2% vs 2.6%; *P*=0.002 bimatoprost vs latanoprost, *P*=0.025 bimatoprost vs timolol). The difference between the rate of pruritus between the latanoprost and timolol GFS groups was not found to be statistically significant (*P*=0.493).
Safety/Adverse Events				
Honrubia et al[51] 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	MA of 13 RCT's 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. The use of latanoprost was associated with a lower incidence of conjunctival hyperemia compared with bimatoprost (OR, 0.32; 95% CI, 0.24 to 0.42; *P*<0.00001). The use of latanoprost was also associated with a lower incidence of conjunctival hyperemia compared with 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[52]	DB, PC, RCT, XO	N=24	Primary: Mean morning	Primary: The difference in mean morning peak expiratory flow volume in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Latanoprost 0.005% 1 drop in both eyes QD vs placebo 1 drop in both eyes	Patients ≥18 years of age, diagnosis of asthma with no exacerbations in three months prior to enrollment, FEV_1 70% to 90% of predicted, 10% reversibility of FEV_1 after inhalation of albuterol	Two six-day treatment periods separated by a two week washout	peak expiratory flow volume, calculated across days one to five Secondary: Mean evening peak expiratory flow volume, methacholine provocation tests, consumption of albuterol	latanoprost and placebo group 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 in the latanoprost and placebo group 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 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[53] Tafluprost 0.0015% 1 drop in the affected eye(s) QD 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 with best-corrected visual acuity 20/40 or better, at least mild dry eye according to OSDI score and/or corneal fluorescein staining in at least one eye, IOP controlled with latanoprost	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 decreased significantly 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 TBUT 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	within previous month			The OSDI questionnaire showed a lower incidence of mild dry eye complaints after 12 weeks of tafluprost treatment (26.7 vs 53.3%; *P* value not reported). The OSSG questionnaire revealed that 40.0% of patients felt dry eye symptoms some of the time at baseline, while 12 weeks after switching to tafluprost, 26.7% of patients continued to report these symptoms (*P* value not reported).
Lewis et al[54] Travoprost 0.004% with benzalkonium chloride 1 drop in the affected eye(s) QPM vs travoprost 0.004% without benzalkonium chloride 1 drop in the affected eye(s) QPM	DB, MC, PG, RCT Adult patients with open-angle glaucoma or ocular hypertension	N=690 3 months	Primary: Equivalence of IOP taken at 8 AM, 10 AM, and 9 PM at two, six, and 12 weeks Secondary: Adverse events	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 0.4; *P*=0.9501) and 0.1 mm Hg at 4 PM (95% CI, -0.3 to 0.5; *P*=0.7003). Secondary: Incidence of 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[55] Travoprost 0.004% without benzalkonium chloride 1 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	MC, OL, PRO Patients with open-angle glaucoma or ocular hypertension unable to tolerate latanoprost or bimatoprost, or judged by their clinician to be good candidates for travoprost	N=691 12 weeks	Primary: Change in ODSI scores Secondary: IOP, conjunctival hyperemia grading and adverse effects	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 which showed statistically significant improvements 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
regimens.	benzalkonium chloride-free solution			Secondary: A significant decrease in IOP was observed after changing from latanoprost to travoprost (*P*<0.001), but not from bimatoprost to travoprost (*P*=0.5245). Both groups previously treated with bimatoprost and latanoprost showed a significant decrease in hyperemia severity grading at week 12 (*P*<0.001). Commonly reported adverse events with travoprost without benzalkonium chloride were conjunctival hyperemia (6%) and change in visual acuity (4%). Patient preference survey found that 72.4% of patients preferred travoprost without benzalkonium chloride compared to 27.6% who preferred prior 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, FEV_1=forced expiratory volume in 1 second, GFS=gel forming solution, MA=meta-analysis, MC=multicenter, mm HG=millimeters of mercury, 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, SD=standard deviation, SR=systematic review, WMD=weighted mean difference, XO=crossover
Other abbreviations: BP=blood pressure, CAI= carbonic anhydrase inhibitor, CCT=central corneal thickness, HR=heart rate, PGA=prostaglandin analogue, OSDI=ocular surface disease index, OSSG=ocular surface symptoms in glaucoma

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Products					
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	Not reported	Not reported	C	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	safety concerns related to increased pigmentation following chronic use.				
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 c dose adjustment required.	C	Unknown

Adverse Drug Events

The most commonly reported adverse events of the ophthalmic prostaglandin analogues include burning/stinging, hyperemia, iris pigmentation changes, and growth and darkening of eyelashes.

Table 6. Adverse Drug Events[1-5]

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	-	-	-

Adverse Events	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Muscle, joint, back pain	-	1 to 2	-	1 to 5
Ocular				
Abnormal vision	-	-	-	1 to 4
Allergic conjunctivitis	1 to 3	-	-	-
Asthenopia	1 to 3	-	-	-
Blepharitis	3 to 10	-	-	1 to 4
Blurred vision	-	5 to 15	2	1 to 4
Burning/stinging	3 to 10	5 to 15	7	-
Cataract	3 to 10	-	3	1 to 4
Conjunctival edema	1 to 3	-	-	-
Conjunctival hyperemia	-	-	4 to 20	-
Conjunctivitis	-	-	5	1 to 4
Corneal edema	-	✔	-	-
Corneal staining	-	-	-	1 to 4
Decreased visual acuity	-	-	-	5 to 10
Dryness/dry eye	3 to 10	1 to 4	3	1 to 4
Eye discharge	1 to 3	-	-	-
Eye discomfort	-	-	-	5 to 10
Eye disorder	-	-	-	1 to 4
Eye pain	3 to 10	1 to 4	3	5 to 10
Flare	-	-	-	1 to 4
Foreign body sensation	3 to 10	5 to 15	-	5 to 10
Herpes keratitis	-	✔	-	-
Hyperemia	15 to 45	5 to 15	-	30 to 50
Increased eyelash growth	15 to 45	✔	-	✔
Increased eyelash pigmentation	3 to 10	✔	2	✔
Increased iris pigmentation	1 to 3	5 to 15	-	1 to 4
Increased periocular skin pigmentation	3 to 10	✔	-	✔
Iritis	-	✔	-	-
Keratitis	-	✔	-	-
Lid crusting	-	1 to 4	-	1 to 4
Lid discomfort/pain	-	1 to 4	-	-
Lid edema	-	1 to 4	-	-
Lid erythema	3 to 10	1 to 4	-	-
Macular edema	✔	✔	-	-
Ocular irritation	3 to 10	-	-	-
Ocular pruritus	15 to 45	5 to 15	5	5-10
Photophobia	1 to 3	1 to 4	-	1 to 4
Subconjunctival hemorrhage	-	-	-	1 to 4
Superficial punctate keratitis	3 to 10	5 to 15	-	1 to 4
Tearing	1 to 3	1 to 4	-	1 to 4
Visual disturbance	3 to 10	-	-	-
Respiratory				
Asthma exacerbation	-	✔	-	-
Bronchitis	-	-	-	1 to 5
Common cold	-	-	4	-
Cough increased	-	-	3	-
Sinusitis	-	-	-	1 to 5
Miscellaneous				
Abnormal liver function tests	1 to 5	-	-	-
Accidental injury	-	-	-	1 to 5

Adverse Events	Bimatoprost	Latanoprost	Tafluprost	Travoprost
Hirsutism	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 / Precautions[1-5]

The use of ophthalmic prostaglandin analogues in patients with known hypersensitivity to any component of the preparation is contraindicated.

The ophthalmic prostaglandin analogues have been associated with changes to pigmented tissues. The most frequently reported areas have been the iris, periorbital tissue (eyelid), and eyelashes. Increases in eyelash growth and number of eyelashes have also been reported. Pigmentation is expected to increase with continued use of these products.

Pigmentation changes in the iris are believed to be due to increased melanin content, resulting in increased brown color of the iris. After discontinuation of treatment, iris pigment changes are likely to be permanent. Iris pigment changes have not progressed upon discontinuation of treatment.

Eyelid skin darkening has been reported in association with the use of the ophthalmic prostaglandin analogues. These changes may be reversible in some patients.

Eyelashes and vellus hair may gradually change in the treated eyes. Changes include increased length, thickness, pigmentation, number of lashes or hairs, and misdirected growth of eyelashes. Changes are usually reversible upon treatment discontinuation.

Patients only receiving treatment in one eye with ophthalmic prostaglandin analogues should be informed that changes will only occur in the treated eye. Treatment may result in disparities in the appearances of both eyes.

The ophthalmic prostaglandin analogues should generally not be used in patients with active intraocular inflammation (iritis/uveitis) and should be used with caution in patients with a history of intraocular inflammation.

Macular edema and cystoid macular edema have been reported with the use of ophthalmic prostaglandin analogues. These cases have mainly been seen in patients with aphakia or pseudophakia, or patients with known risk factors for macular edema. Prostaglandin analogues should be used with caution in patients without an intact posterior capsule or are at risk for developing macular edema.

The ophthalmic prostaglandin analogues are not approved for use in the treatment of angle closure, inflammatory, or neovascular glaucoma.

Patients using multiple-dose containers are at an increased risk for bacterial keratitis. Typically, these containers have been inadvertently contaminated by the patients who had concurrent corneal disease or disruption of the ocular epithelial surface.

Contact lenses should be removed prior to the use of prostaglandin analogues. They may be inserted 15 minutes after administration.

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.[56]

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.[2]

Dosage and Administration

Table 7. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Products			
Bimatoprost	Open-angle glaucoma: Ophthalmic solution: instill 1 drop into affected eye(s) QD in the evening; the dosage should not exceed once daily Ocular hypertension: Ophthalmic solution: instill 1 drop into affected eye(s) QD 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	Open-angle glaucoma: Ophthalmic solution: instill 1 drop into affected eye(s) QD in the evening; the dosage should not exceed once daily Ocular hypertension: Ophthalmic solution: instill 1 drop into affected eye(s) QD 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	Open-angle glaucoma: Ophthalmic solution: instill 1 drop into affected eye(s) QD in the evening; the dosage should not exceed once daily Ocular hypertension: Ophthalmic solution: instill 1 drop into affected eye(s) QD 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	Open-angle glaucoma: Ophthalmic solution: instill 1 drop into affected eye(s) QD	Use in pediatric patients <16 years is not recommended due to	Ophthalmic solution: 0.004% (2.5, 5 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	in the evening; the dosage should not exceed once daily Ocular hypertension: Ophthalmic solution: instill 1 drop into affected eye(s) QD in the evening; the dosage should not exceed once daily	potential safety concerns related to increased pigmentation following long-term chronic use.	

Drug regimen abbreviations: QD=once daily

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Glaucoma Panel, Preferred Practice Patterns Committee. Primary Open-Angle Glaucoma (2010)**[9]	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. • Alpha$_2$-adrenergic agonists, ophthalmic and oral carbonic anhydrase inhibitors, and parasympathomimetics are less frequently used. • If a drug fails to reduce IOP, 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 incisional surgery.
American Optometric Association: **Clinical Practice Guidelines: Care of the Patient with Open Angle Glaucoma (2010)**[10]	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 intraocular pressure (IOP) by up to 35 percent

Clinical Guideline	Recommendations
	when given once daily and is equal to or more effective than 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 percent. • Travoprost 0.004% has a similar effectiveness to latanoprost. It reduces IOP up to 33 percent. 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. • An epinephrine prodrug, dipivefrin, is available in a 0.1% concentration and is the drug of choice among epinephrine. 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 and prevents the acute spike in IOP that may occur after argon laser trabeculoplasty (ALT) and other laser procedures. By lowering IOP by 25 percent, 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. In a 0.2% solution, brimonidine 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 20 to 40%, but is 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. The IOP-lowering effect of brinzolamide appears to be the same. Both have additive effects when used with timolol. Miotic agents

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
• Pilocarpine is the miotic drug most frequently in glaucoma in doses ranging from 1.0% to 4%; the duration of action is at least six hours.
• Pilocarpine also is available in a 4% gel preparation.
</td></tr>
<tr><td>National Institute for Clinical Excellence: Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension (2009)[11]</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 antagonist or ophthalmic prostaglandin analogues.
• 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 analogue or ophthalmic sympathomimetic) when medication intolerance to current medication is experienced or target intraocular pressure (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).

<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 analogue</td><td>Prosta-glandin analogue</td><td>Prosta-glandin analogue</td></tr>
</table>
†If beta-blockers are contraindicated offer a prostaglandin analogue.
• Patients should be referred to an ophthalmologist when target IOP reduction cannot be achieved.

<u>Treatment of patients with open angle glaucoma</u>
• 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.
• Patients should be offered surgery along with medication if they are at risk for vision loss despite treatment.
</td></tr>
</table>

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

Conclusions

The four ophthalmic prostaglandin analogues currently available in the United States are bimatoprost (Lumigan®), latanoprost (Xalatan®), tafluprost (Zioptan®) and travoprost (Travatan Z®). They are all Food and Drug Administration (FDA)-approved for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1-4] All of the agents within this class are administered once daily, and latanoprost is the only product that is currently available generically.[5] In addition to conjunctival hyperemia, ocular side effects of 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 as a class are considered to be better tolerated compared to other classes of medications used for the management of glaucoma. Tafluprost, approved by the FDA in February 2012, 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 analogue products.[5,45] Bimatoprost has been shown to have the greatest IOP-reducing effect among the prostaglandin analogues and is available as both a 0.01% and 0.03% solution.[1,5,14-15,17-18,20,26-27] While study results have demonstrated differences in IOP-lowering ability among the other agents within the class, the differences are generally small and the clinical significance of these changes remains to be established.

The current consensus guidelines by the American Academy of Ophthalmology and the American Optometric Association both support the use of ophthalmic β adrenergic antagonists or 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.[9,10] Furthermore, the guidelines do not recommend any one ophthalmic prostaglandin analogue over another. The results from various meta-analyses have demonstrated that prostaglandin analogues are the most effective class of medications for reducing IOP and can reduce IOP by up to 35% and to a further extent compared alpha$_2$-adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors and other recommended therapies.[14,15] Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory.

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