Therapeutic Class Overview
Ophthalmic Glaucoma Combinations

Therapeutic Class

- **Overview/Summary:** Treatment of glaucoma currently focuses on decreasing IOP by one of three methods: laser therapy, surgery, or medical intervention.[1-4] Medical intervention includes five ophthalmic classes of drugs used for the long-term management of glaucoma: alpha$_2$ adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics, and prostaglandin analogues. These treatments reduce IOP by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow. Parasympathomimetics and prostaglandin analogues increase aqueous outflow, while beta-adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha$_2$ adrenergic agonists both decrease the amount of aqueous humor formed and increase its outflow. [1] Combigan® combines the action of a beta adrenergic antagonist (timolol maleate) and an alpha$_2$ adrenergic agonist (brimonidine), while Cosopt® contains the same beta adrenergic antagonist (timolol maleate) in combination with a carbonic anhydrase inhibitor (dorzolamide). Cosopt PF® contains the same active ingredients as Cosopt® in a preservative-free formulation.[10] Simbrinza® combines the action of a carbonic anhydrase inhibitor (brinzolamide) and an alpha$_2$ adrenergic agonist (brimonidine)[11] The ophthalmic glaucoma combination agents are Food and Drug Administration approved for reducing elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP or in patients who are insufficiently responsive to beta adrenergic antagonists.[8-11] Due to the potential systemic absorption of the ophthalmic glaucoma combination agents, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration.[8-11] The ophthalmic combination products are most commonly associated with ocular adverse effects, such as blurred vision, conjunctival hyperemia, discharge and dry eye. Brimonidine/timolol maleate (Combigan®) and dorzolamide/timolol maleate (Cosopt® and Cosopt PF®) are administered as one drop the affected eye(s) twice daily (approximately 12 hours apart), while brinzolamide/brimonidine (Simbrinza®) is administered as one drop in the affected eye(s) three times daily.[8-11]

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Brimonidine/ timolol maleate (Combigan®*)	Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled intraocular pressure	Ophthalmic solution: 0.2%/0.5% (5, 10 mL)	✔
Brinzolamide/ brimonidine (Simbrinza®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 1%/0.2% (10 mL)	-
Dorzolamide/ timolol maleate (Cosopt*®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers†	Ophthalmic solution: 2%/0.5% (10 mL)	✔
Dorzolamide/ timolol maleate (Cosopt PF®*)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers†	Ophthalmic solution: 2%/0.5% (0.2 mL single-use vials)	✔

*Available generically in one dosage form or strength.
†Patients who failed to achieve target intraocular pressure after multiple measurements over time.

Evidence-based Medicine

- In trials involving ophthalmic timolol maleate 0.5% and ophthalmic dorzolamide 2.0% it was demonstrated that the addition of timolol maleate 0.5% to dorzolamide 2.0% provided additional reductions in intraocular pressure (IOP) and the use of the fixed dose combination did not cause significant differences in the reduction of IOP from baseline when compared to using the agents separately.[13,14]
- Trials comparing ophthalmic dorzolamide/timolol maleate to ophthalmic bimatoprost 0.03% demonstrated that both groups significantly decreased IOP from baseline but showed conflicting results regarding differences between the groups. Two trials demonstrated that ophthalmic bimatoprost 0.03% decreased IOP from baseline significantly more than ophthalmic dorzolamide/timolol maleate; however, only one trial demonstrated the difference after six months of treatment to be statistically significant.[15-17]
- When ophthalmic dorzolamide/timolol maleate was compared to ophthalmic latanoprost, it was also demonstrated that both groups significantly decreased IOP from baseline, but conflicting results were observed regarding the difference in IOP reduction between groups.[18-20] Two trials did demonstrated that ophthalmic dorzolamide/timolol maleate produced significantly higher reductions in IOP (after two weeks of treatment in one study and after three months of treatment in the second).[18,20]
- In a trial comparing ophthalmic dorzolamide/timolol maleate to the individual components, it was demonstrated that the combination product was more effective at reducing IOP from baseline at all time periods over three months of treatment.[21] When ophthalmic dorzolamide/timolol maleate was compared to ophthalmic brimonidine/timolol maleate it was demonstrated that both groups significantly reduced IOP form baseline (P<0.001) and the difference between groups was not found to be significant (P value not reported).[22,23]
- In one study comparing dorzolamide/timolol preservative-free and preservative-containing formulations, both formulations were found to be clinically equivalent with an estimated difference of 0.31 mm Hg between the treatment groups for the change from baseline in trough IOP at week 12.[24] In a second study evaluating the efficacy of dorzolamide/timolol preservative-free, patients treated with the preservative-free formulation exhibited a mean absolute reduction from baseline in IOP of 4.1 mm Hg.[25]
- Two studies compared the efficacy of brinzolamide/brimonidine in a fixed-dose combination to the efficacy of brinzolamide or brimonidine as monotherapy. Both studies demonstrated that treatment with brinzolamide/brimonidine as a fixed-dose combination resulted in a significantly greater reduction in IOP compared to monotherapy with either agent (P<0.005 for both studies).[26,27]
- Two meta-analyses have analyzed patients with open-angle glaucoma or ocular hypertension and included treatment with ophthalmic glaucoma combinations and prostaglandin analogues.[28,29] Specifically, when treatment with ophthalmic dorzolamide in combination with ophthalmic timolol maleate both as concomitant and fixed-dose administration) was compared to treatment with ophthalmic latanoprost, changes in mean reductions in IOP were comparable between the two groups at one (P=0.08), two (P=0.19), three (P=0.71), and six (P=0.28) months of therapy.[28]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Open-angle Primary Glaucoma[3,4,39]
        - If target intraocular pressure (IOP) is not achieved by one medication, additional medications, combination therapies, or switching of treatments may be considered to reach the target IOP.
        - First-line medication therapy should consist of ophthalmic beta-blockers or ophthalmic prostaglandin analogues.
        - Ophthalmic carbonic anhydrase inhibitors and ophthalmic sympathomimetics should be considered second-line medication therapy.
        - If a drug fails to reduce IOP despite adherence to treatment, it should be replaced with an alternative agent until effective medical treatment is achieved.

  - If a single medication effectively reduces IOP but the target IOP has not been achieved, combination therapy or switching to an alternative medication should be considered.
  - When used as monotherapy, brimonidine is less effective than prostaglandin analogs but additive with timolol and latanoprost and can be used as combination or replacement therapy.
  - Dorzolamide and brinzolamide have similar IOP-lowering effects and have additive effects when used with timolol.
  - Clinical studies have demonstrated that combination therapy is more effective in reducing IOP compared to monotherapy with either agent alone.
- Other Key Facts:
  - Brimonidine/timolol maleate (Combigan®) and dorzolamide/timolol maleate (Cosopt®, Cosopt PF®) are dosed twice daily approximately 12 hours apart.
  - Brinzolamide/brimonidine (Simbrinza®) is dosed three times daily.
  - Brimonidine/timolol maleate (Combigan®) and dorzolamide/timolol maleate (Cosopt®, Cosopt PF®) are available generically, while brinzolamide/brimonidine (Simbrinza®) is available as a branded product, only.

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Therapeutic Class Review
Ophthalmic Glaucoma Combinations

Overview/Summary

Glaucoma is an optic neuropathy which causes gradual degeneration of the cells making up the optic nerve. Glaucoma initially manifests as visual field loss and may progress to blindness. It is the leading cause of irreversible blindness and second leading cause of vision loss in the world.[1] There are four distinct types of glaucoma: primary open-angle, acute angle-closure, secondary, and congenital. The most common of which is open-angle glaucoma.[1] Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness. The exact etiology of open-angle glaucoma is unknown. Risk factors have been well studied and include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, or a central corneal thickness less than 545 micrometers.[2-4] Other possible risk factors that have been studied include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus, and hypothyroidism.[5-7]

Of the major risk factors associated with the development of glaucoma, IOP is treatable. Evidence shows that lowering IOP inhibits the progression of optic nerve damage.[1-4] Patients with a raised IOP may receive treatment even if they have no visual field loss or optic nerve damage. An IOP 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.[1] Patients' target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[3,4]

Treatment of glaucoma currently focuses on decreasing IOP by one of three methods: laser therapy, surgery, or medical intervention.[1-4] Medical intervention includes five ophthalmic classes of drugs used for the long-term management of glaucoma: alpha$_2$ adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics, and prostaglandin analogues. These treatments reduce IOP by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow. Parasympathomimetics and prostaglandin analogues increase aqueous outflow, while beta-adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha$_2$ adrenergic agonists both decrease the amount of aqueous humor formed and increase its outflow.[1] Consensus guidelines recommend beta-adrenergic antagonists and prostaglandin analogues as first-line medication therapy. 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.[3,4]

Included in this review are the ophthalmic glaucoma combination medications which include Combigan® (brimonidine/timolol maleate), Cosopt® (dorzolamide/timolol maleate), Cosopt PF® (dorzolamide/timolol maleate) and Simbrenza® (brinzolamide/brimonidine).[8-11] Combigan® combines the action of a beta adrenergic antagonist (timolol maleate) and an alpha$_2$ adrenergic agonist (brimonidine), and is currently available generically. Cosopt® contains the same beta adrenergic antagonist (timolol maleate) in combination with a carbonic anhydrase inhibitor (dorzolamide), and is currently available generically. Cosopt PF® contains the same active ingredients as Cosopt® in a preservative-free formulation and it is currently available generically.[10] Simbrinza® combines the action of a carbonic anhydrase inhibitor (brinzolamide) and an alpha$_2$ adrenergic agonist (brimonidine), and is currently available as a branded product only.[11] The ophthalmic glaucoma combination agents are Food and Drug Administration approved for reducing elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP or in patients who are insufficiently responsive to beta adrenergic antagonists.[8-11] The ophthalmic glaucoma combination agents are not specifically addressed within the current clinical guidelines; however, ophthalmic beta adrenergic antagonists and prostaglandins are recommended as first-line therapy; and alpha$_2$ adrenergic agonists, carbonic anhydrase inhibitors, and parasympathomimetics are typically utilized as second-line therapies.[3,4]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Brimonidine/timolol maleate (Combigan®*)	Ophthalmic glaucoma combinations	✔
Brinzolamide/brimonidine (Simbrinza®)	Ophthalmic glaucoma combinations	-
Dorzolamide/timolol maleate (Cosopt®)	Ophthalmic glaucoma combinations	✔
Dorzolamide/timolol maleate (Cosopt PF®*)	Ophthalmic glaucoma combinations	✔

*Available generically in one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[8-11]

Generic Name	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled intraocular pressure	✔			
Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		✔		
Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers*			✔ *	✔ *

*Patients who failed to achieve target intraocular pressure after multiple measurements over time.

Pharmacokinetics

After twice-daily topical dosing of Combigan® in normal volunteers for seven days, peak plasma brimonidine and timolol maleate concentrations were 30 and 400 pg/mL, respectively.[8] Plasma concentrations peaked at one to four, and one to three hours post dose for brimonidine and timolol maleate. Additionally, in a parallel trial in patients dosed twice-daily with Combigan®, three-times daily with brimonidine 0.2%, or twice-daily with timolol maleate 0.5%, one hour post dose plasma concentrations of timolol maleate and brimonidine were approximately 30 to 40% lower with Combigan® than their respective monotherapy values. The lower plasma brimonidine concentrations with Combigan® are believed to be due to the twice-daily vs three-times daily dosing.

Table 3. Pharmacokinetics[8-12]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Brimonidine/ timolol maleate	Rapidly absorbed (percent not reported)	Yes (percent not reported)/75	Not reported/not reported	7/3
Brinzolamide/ brimonidine	Absorbed (percent not reported)	Yes (percent not reported)/74	N-desethyl brinzolamide	2,264/3
Dorzolamide/ timolol maleate	Absorbed (percent not reported	Significant (percent not reported)	N-desethyl-dorzolamide	2 to 4/ undetermined

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dorzolamide/ timolol maleate PF	Absorbed (percent not reported	Significant (percent not reported)	N-desethyl-dorzolamide	2 to 4/ undetermined

Clinical Trials

In trials involving ophthalmic timolol maleate 0.5% and ophthalmic dorzolamide 2.0% it was demonstrated that the addition of timolol maleate 0.5% to dorzolamide 2.0% provided additional reductions in intraocular pressure (IOP) and the use of the fixed dose combination did not cause significant differences in the reduction of IOP from baseline when compared to using the agents separately.[13,14] Trials comparing ophthalmic dorzolamide/timolol maleate to ophthalmic bimatoprost 0.03% demonstrated that both groups significantly decreased IOP from baseline but showed conflicting results regarding differences between the groups. Two trials demonstrated that ophthalmic bimatoprost 0.03% decreased IOP from baseline significantly more than ophthalmic dorzolamide/timolol maleate; however, only one trial demonstrated the difference after six months of treatment to be statistically significant.[15-17] When ophthalmic dorzolamide/timolol maleate was compared to ophthalmic latanoprost, it was also demonstrated that both groups significantly decreased IOP from baseline, but conflicting results were observed regarding the difference in IOP reduction between groups.[18-20] Two trials did demonstrated that ophthalmic dorzolamide/timolol maleate produced significantly higher reductions in IOP (after two weeks of treatment in one study and after three months of treatment in the second).[18,20]

In a trial comparing ophthalmic dorzolamide/timolol maleate to the individual components, it was demonstrated that the combination product was more effective at reducing IOP from baseline at all time periods over three months of treatment.[21] When ophthalmic dorzolamide/timolol maleate was compared to ophthalmic brimonidine/timolol maleate it was demonstrated that both groups significantly reduced IOP form baseline (P<0.001) and the difference between groups was not found to be significant (P value not reported).[22,23]

In one study comparing ophthalmic dorzolamide/timolol preservative-free and preservative-containing formulations, the investigators found that treatment with both formulations were clinically equivalent with an estimated difference of 0.31 mm Hg between the treatment groups for the change from baseline in trough IOP at week 12.[24] In a second study evaluating the efficacy of ophthalmic dorzolamide/timolol preservative-free, patients treated with the preservative-free formulation exhibited a mean absolute reduction from baseline in IOP of 4.1 mm Hg.[25]

Two studies compared the efficacy of ophthalmic brinzolamide/brimonidine in a fixed-dose combination to the efficacy of ophthalmic brinzolamide or ophthalmic brimonidine as monotherapy. Both studies demonstrated that treatment with ophthalmic brinzolamide/brimonidine as a fixed-dose combination resulted in a significantly greater reduction in IOP compared to monotherapy with either agent (P<0.005 for both studies).[26,27]

Two meta-analyses have analyzed patients with open-angle glaucoma or ocular hypertension and included treatment with ophthalmic glaucoma combinations and prostaglandin analogues.[28,29] Specifically, when treatment with ophthalmic dorzolamide in combination with ophthalmic timolol maleate both as concomitant and fixed-dose administration) was compared to treatment with ophthalmic latanoprost, changes in mean reductions in IOP were comparable between the two groups at one (P=0.08), two (P=0.19), three (P=0.71), and six (P=0.28) months of therapy.[28]

Table 4. Clinical Trials

<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>Sharpe et al[15]

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

vs

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

Patients ≥18 years of age, bilateral open-angle glaucoma, IOP between 22 mm Hg 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

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

Secondary:
IOP at individual time points, mean diurnal range, mean peak IOP, reduction of IOP from baseline, visual acuity, 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><th colspan="5">Absolute IOPs (mm Hg±SD)</th></tr>
<tr><th>Time</th><th>Baseline</th><th>Dorzolamide/timolol</th><th>Bimatoprost</th><th>P value</th></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 (P<0.0001). Overall there were 17 ocular adverse events with dorzolamide/timolol compared to five with bimatoprost.</td>
</tr>
<tr>
<td>Spaeth et al[30]

Brimonidine/timolol 0.2%/0.05% ophthalmic solution (Combigan®) BID</td>
<td>DB, PG, RCT

Pooled post-hoc analysis of two 12-month trials

Patients with</td>
<td>N=1,159

12 months</td>
<td>Primary:
Control of IOP fluctuations and IOP (defined as IOP fluctuation of ≤2 mm Hg plus attainment of target</td>
<td>Primary:
The proportion of patients that achieved a target mean diurnal IOP <18 mm Hg was statistically significantly greater in the fixed brimonidine/timolol group compared to patients treated with the individual components.

There was a trend observed toward a lower proportion of patients in the fixed brimonidine/timolol group having a short-term daily IOP fluctuation ≤2 mm Hg</td>
</tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs brimonidine 0.2% ophthalmic solution TID vs timolol 0.5% ophthalmic solution BID	glaucoma or ocular hypertension		mean IOP of <18 mm Hg) Secondary: Not reported	(*P*≤0.88). A statistically significantly higher proportion of patients in the fixed brimonidine/timolol treatment group had a daily IOP fluctuation ≤2 mm Hg at each follow-up visit compared to the brimonidine group (*P*≤0.002). There was no significant difference in daily IOP fluctuation observed between the fixed brimonidine/timolol treatment group compared to the timolol group at weeks two and six or at month six. At months three, nine and 12, patients treated with timolol were statistically significantly more likely to have daily IOP fluctuations ≤2 mm Hg compared to patients treated with fixed brimonidine/timolol (*P*≤0.02). There was no significant difference in the proportion of patients with long-term IOP fluctuations ≤2 mm Hg between the brimonidine/timolol and brimonidine treatment groups at each hour (8AM, 10AM, 3PM and 5PM; *P*≤0.023). The differences in long-term IOP fluctuations between brimonidine/timolol and timolol treatment groups were not significant at 10AM, 3PM or 5PM; however, there was a statistically significantly greater proportion of patients treated with fixed brimonidine/timolol who had long-term IOP fluctuations ≤2 mm Hg at the 8AM measurement compared to the timolol group (*P*=0.14). At each follow-up visit, a significantly greater proportion of patients in the fixed brimonidine/timolol group achieved both a mean diurnal IOP <18 mm Hg and daily IOP fluctuation ≤2 mm Hg compared to the timolol group (*P*≤0.044). A significantly greater proportion of patients treated with fixed brimonidine/timolol demonstrated both mean diurnal IOP <18 mm Hg and short-term IOP fluctuation ≤3 or ≤4 mm Hg at each follow-up visit compared to either the brimonidine or timolol groups. At each hour, a significantly greater proportion of patients in the fixed brimonidine/timolol treatment group achieved both mean IOP <18 mm Hg at that hour across visits and long-term IOP fluctuation ≤2 mm Hg compared to patients treated with timolol (*P*≤0.006). Patients in the fixed brimonidine/timolol group were also significantly more likely than patients in the brimonidine group to achieve both IOP <18 mm Hg and long-term IOP fluctuation ≤2 mm Hg at 8AM, 10AM, 3PM and 4PM (*P*≤0.003). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Katz et al[26] Brinzolamide/ brimonidine 1%/0.2% fixed-combination 1 drop into affected eye(s) TID vs brinzolamide 1% 1 drop into affected eye(s) TID vs brimonidine 0.2% 1 drop into affected eye(s) TID	DB, PG, MC, RCT Patients ≥18 years of age with a clinical diagnosis of open-angle glaucoma or ocular hypertension	N=660 3 months	Primary: Mean IOP at three month visit at all time points (8AM, 10AM, 3PM and 5PM) Secondary: Mean IOP at the two week and six week visits for all time points (8AM, 10AM, 3PM and 5PM)	Primary: The mean IOP of the brinzolamide/brimonidine treatment group was significantly lower than that of the brinzolamide or brimonidine groups ($P \leq 0.002$). Results of the sensitivity analysis were similar, with the mean IOP of the brinzolamide/brimonidine treatment group significantly lower at each time point and visit ($P \leq 0.003$) than the mean IOP of the brinzolamide or brimonidine treatment groups. When patients were stratified according to lower and higher baseline IOP, the mean IOP was lower with brinzolamide/brimonidine compared to brinzolamide or brimonidine at all four time points for both strata. Secondary: The mean IOP of the brinzolamide/brimonidine treatment group was significantly lower at all time points for the two week and six week visits compared to the brinzolamide or brimonidine treatment groups ($P<0.001$). There were a total of 10 serious adverse events, one of which was determined to be related to treatment; this was a case of chest pain of moderate intensity that occurred in a patient in the brinzolamide treatment group. A total of 129 patients experienced one or more treatment-related adverse events (brinzolamide/brimonidine, 22.9% vs brinzolamide, 18.9% vs brimonidine 17.3%; $P=0.31$)
Nguyen et al[27] Brinzolamide/ brimonidine 1%/0.2% fixed-combination 1 drop into affected eye(s) TID vs brinzolamide 1% 1 drop into affected eye(s) TID vs	DB, ES, MC, PG Patients with open-angle glaucoma or ocular hypertension with IOP between 24 and 36 mm Hg at the 8AM and 10AM time points at the first and second eligibility visits, as well as IOP ≤36 mm Hg in both eyes at all time points	N=615 3 months	Primary: Mean IOP at three-month visit at each of the four time points (8AM, 10AM, 3PM, 5PM) Secondary: Mean IOP at two- and six-week visits for all time points (8AM, 10AM, 3PM, 5PM)	Primary: The mean IOP at the three-month visit was significantly lower in the brinzolamide/brimonidine fixed combination group compared to either the brinzolamide or brimonidine groups at all four time points ($P \leq 0.005$). Secondary: The mean IOP at the two- and six-week visits was significantly lower at all time points in the brinzolamide/brimonidine fixed combination group compared to either the brinzolamide ($P \leq 0.01$) or brimonidine treatment groups ($P<0.0001$; six-week data not shown). At the three-month visit, the change in IOP observed in the brinzolamide/brimonidine fixed combination group ranged from a 3.7% improvement to a 13.4% improvement in % IOP reduction from baseline. These reductions in the brinzolamide/brimonidine fixed combination group ranged from

<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>brimonidine 0.2% 1 drop into affected eye(s) TID</td><td></td><td></td><td></td><td>5.4 to 8.4 mm Hg (across all time points), from 4.2 to 5.7 mm Hg in the brinzolamide group and from 3.1 to 6.5 mm Hg in the brimonidine group.</td></tr>
<tr><td>Michaud et al[31]

Brinzolamide 1% 1 drop into affected eye(s) BID and timolol 0.5% 1 drop into affected eye(s) BID

vs

dorzolamide 2% 1 drop into affected eye(s) BID and timolol 0.5% 1 drop into affected eye(s) BID</td><td>AC, DB, MC, PG, RCT

Patients 21 years of age or older with a diagnoses of primary open-angle glaucoma or ocular hypertension and currently not controlled on timolol BID</td><td>N=241

3 months</td><td>Primary:
Changes in IOP from baseline at one, two and three months and assessment of safety and tolerability

Secondary:
Not reported</td><td>Primary:
Both treatment regimens demonstrated statistically significant reductions in IOP from baseline at all time points (P<0.001).

Changes in IOP
<table><tr><th rowspan="2">Time Period</th><th colspan="2">Baseline</th><th colspan="2">Month 1</th><th colspan="2">Month 2</th><th colspan="2">Month 3</th></tr><tr><th>9 AM</th><th>11 AM</th><th>9 AM</th><th>11 AM</th><th>9 AM</th><th>11 AM</th><th>9 AM</th><th>11 AM</th></tr><tr><td>Brinzolamide and timolol</td><td>25.2</td><td>24.1</td><td>-3.6</td><td>-4.9</td><td>-4.6</td><td>-5.3</td><td>-4.3</td><td>-4.9</td></tr><tr><td>Dorzolamide and timolol</td><td>25.8</td><td>24.1</td><td>-3.6</td><td>-4.6</td><td>-4.1</td><td>-5.1</td><td>-4.3</td><td>-5.0</td></tr><tr><td>Difference in treatment groups</td><td>-</td><td>-</td><td>0.0</td><td>-0.3</td><td>-0.4</td><td>-0.2</td><td>-0.1</td><td>0.2</td></tr></table>
Adverse events were reported in 17/238 (14.7%) patients in the brinzolamide group compared to 40/238 patients in the dorzolamide group (P=0.001). Of the adverse events reported, the only event that occurred significantly more in the brinzolamide group than the dorzolamide group was ocular discomfort (burning and stinging) (2 vs 16; P=0.001).

Other adverse events that occurred in >1% of brinzolamide patients were blurred vision (2%) and taste perversion (3%). In the dorzolamide group, more adverse events were reported and included hyperemia (4%), tearing (3%), pruritus (2%), blurred vision (2%), and taste pervasion (4%).

Secondary:
Not reported</td></tr>
<tr><td>Crichton et al[32]

Dorzolamide/timolol (Cosopt®) 1 drop in each eye twice daily</td><td>MC, OL, PRO

Patients 18 years of age or older, newly diagnosed with open-</td><td>N=164

12 weeks</td><td>Primary:
Absolute and percent change in IOP from baseline to six and 12</td><td>Primary:
At week-six, the mean absolute and percent IOP reduction for the total population was 11.1 and 13.9%, respectively.

Between weeks six and 12, the mean absolute and percent changes in IOP were</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>for 6 weeks, if IOP goal was not reached at that time, latanoprost (Xalatan®) was added for another 6 weeks</td><td>angle glaucoma or ocular hypertension, with an IOP of at least 27 mm Hg in at least one eye</td><td></td><td>weeks of treatment

Secondary:
Proportion of patients achieving target IOP, proportion of patients achieving therapeutic response (reduction of 5 mm Hg or 20% in IOP from baseline) at six and 12 weeks, safety</td><td>not significant among patients treated with dorzolamide/timolol. However, patients who had received the additional latanoprost experienced a statistically significant improvement in IOP (mean and percent reductions) between six and 12 weeks of therapy (P<0.05).

Secondary:
IOP reduction of at least 5 mm Hg was achieved by 92.1% of patients at week-six of therapy (P<0.001).

At week-12, an IOP reduction of at least 5 mm Hg or 20% was noted in 97% of patients in the dorzolamide/timolol group and in 87.5% of patients in the dorzolamide/timolol and latanoprost group.

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

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

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

Treatment-related adverse events were reported by 14.0 and 21.4% of patients receiving dorzolamide/timolol and dorzolamide/timolol and latanoprost combination therapy, respectively. Eye disorders and nervous system disorders were the most frequently reported adverse events.</td></tr>
<tr><td>Hartenbaum[13]

Dorzolamide 2% 1 drop into affected eye(s) TID and timolol 0.5% 1 drop into affected eye(s) BID</td><td>ES, OL

Patients 21 to 85 years of age with a diagnosis of open-angle glaucoma or ocular hypertension</td><td>N=95

12 months</td><td>Primary:
Effect on IOP after a failure of monotherapy with dorzolamide

Secondary:</td><td>Primary:
Timolol lowered peak and trough IOP when it was added to dorzolamide monotherapy by 28 and 34% respectably.

<table><tr><th colspan="5">Reduction in IOP</th></tr><tr><th>Time</th><th>Baseline IOP (mm</th><th>Treatment IOP (mm</th><th>Percent Change from</th><th>Percent Change From End of</th></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>who had an IOP >21 mm Hg or <15% decrease in IOP during a trial and required the addition of a second agent</td><td></td><td>Assessment of safety and tolerability</td><td>
<table>
<tr><td></td><td>Hg)</td><td>Hg)</td><td>Baseline (%)</td><td>Monotherapy (%)</td></tr>
<tr><td>Hour 2</td><td>29.3</td><td>19.6</td><td>-32.0</td><td>-20.0</td></tr>
<tr><td>Hour 5</td><td>27.4</td><td>19.6</td><td>-27.0</td><td>-19.0</td></tr>
<tr><td>Hour 9</td><td>26.9</td><td>20.1</td><td>-24.0</td><td>-16.0</td></tr>
</table>

Secondary:
In the test group, 16 patients developed drug related adverse effects during the study. The most common adverse events that were reported in >3% of patients were conjunctivitis (6%), upper respiratory tract infections (5%), headache (5%), influenza (3%), paresthesia (3%), and dyspnea (3%).</td></tr>
<tr><td>Francis et al[14]

Dorzolamide/timolol 2%/0.5% 1 drop into affected eye(s) BID (fixed dose combination group)

vs

timolol 0.5% 1 drop into affected eye(s) BID and dorzolamide 2% 1 drop into affected eye(s) TID (co-administered group)</td><td>Study 1
PRO, RCT

Patients ≥18 years of age with primary open angle glaucoma, ocular hypertension, or pseudoexfoliation glaucoma in either eyes with current treatment of both topical non-selective beta-blocker and topical carbonic anhydrase inhibitor or a fixed dose combination

Study 2
PRO, non-randomized replacement trial

Patients ≥18 years of age with primary open-angle glaucoma or ocular hypertension</td><td>Study 1
N=131 eyes

4 weeks

Study 2
N=404 eyes

4 weeks</td><td>Primary:
Mean change in baseline peak and trough IOP

Secondary:
Not reported</td><td>Primary:
Study 1
Patients in the coadministration group showed a peak IOP change of -0.3 mm Hg (17.6 to 17.3) and a trough IOP change of -0.8 mm Hg (19.8 to 19.0).

In the fixed dose combination group, the change from baseline for peak IOP was -0.8 mm Hg (18.4 to 17.6) and trough was -1.5 mm Hg (21.0 to 19.5).

When compared, all results were not statistically significant (P=0.34 for peak change, P=0.16 for trough change).

Study 2
After patients were switched from dorzolamide and timolol co-administered to a fixed dose combination, they experience a mean change in IOP of 1.7 mm Hg (19.4 to 17.6; P<0.0001).

Secondary:
Not reported</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>or pseudoexfoliation glaucoma; currently on both a topical non-selective beta-blocker and topical carbonic anhydrase inhibitor</td><td></td><td></td><td></td></tr>
<tr><td>Ozturk et al[16]

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

vs

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

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

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

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

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

Conjunctival hyperemia did occur in significantly more patients in the timolol/dorzolamide group than in the bimatoprost group (P=0.02).</td></tr>
<tr><td>Coleman et al[17]

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

vs

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

Diagnosis of open-angle glaucoma, ocular hypertension, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma, baseline IOP of 22 mm Hg to 34 mm Hg after at least two weeks of topical timolol 0.5% therapy</td><td>N=177

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

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

<table>
<tr><th colspan="6">Mean IOP (mm Hg) Change From Baseline</th></tr>
<tr><th>Time</th><th>Treatment Group</th><th>Week 1</th><th>Month 1</th><th>Month 2</th><th>Month 3</th></tr>
<tr><td rowspan="3">8 AM</td><td>Bimatoprost</td><td>-7.6</td><td>-7.1</td><td>-7.2</td><td>-6.8</td></tr>
<tr><td>Dorzolamide /timolol</td><td>-4.4</td><td>-4.8</td><td>-4.8</td><td>-5.0</td></tr>
<tr><td>P value</td><td><0.001</td><td><0.001</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">10 AM</td><td>Bimatoprost</td><td>-6.9</td><td>-6.5</td><td>-6.6</td><td>-6.4</td></tr>
<tr><td>Dorzolamide /timolol</td><td>-5.1</td><td>-5.1</td><td>-5.4</td><td>-5.6</td></tr>
<tr><td>P value</td><td><0.001</td><td>0.007</td><td>0.014</td><td>0.130</td></tr>
</table>

Secondary:
All reported adverse events were mild to moderate.</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Conjunctival hyperemia was reported more commonly in the bimatoprost group compared to the dorzolamide/timolol group (34.0 vs 17.2%; *P*=0.009). Ocular burning, ocular stinging, and taste perversion were the most common events in the dorzolamide/timolol group compared to the bimatoprost group (13.3 vs 2.0%; *P*=0.004, 9 vs 2%; *P*=0.025, 5 vs 0%; *P*=0.027).
Siesky et al[33] Dorzolamide/timolol ophthalmic solution (Cosopt®) BID for 1 month vs brimonidine/timolol 0.2%/0.05% ophthalmic solution (Combigan®) BID for 1 month	DB, PRO, R, XO Patients 30 years of age or older, diagnosed with open angle glaucoma in at least one eye, defined as characteristic glaucomatous visual loss and optic nerve head damage, best corrected visual acuity of at least 20/40 and a baseline IOP well controlled below 22 mm Hg	N=15 3 months (1 month each treatment phase)	Primary: Change from baseline in IOP, blood pressure, ocular perfusion pressure, and retrobulbar hemodynamics Secondary: Not reported	Primary: After one month of treatment, there were no statistically significant differences between dorzolamide/timolol and brimonidine/timolol in effects on IOP, blood pressure, ocular perfusion pressure, and retrobulbar blood flow velocities (*P*>0.05). Secondary: Not reported
Gulkilik et al[34] Dorzolamide/timolol 2%/0.5% ophthalmic solution (Cosopt®) BID for 4 weeks vs brimonidine/timolol 0.2%/0.05% ophthalmic solution (Combigan®) BID for 4 weeks	PRO, XO Patients 18 years of age or older, diagnosed with primary open angle glaucoma, visual acuity of at least 5/10 and a baseline IOP between 22 and 34 mm Hg	N=42 (42 eyes) 12 weeks (4 weeks each treatment phase, 4 week wash-out phase)	Primary: Change from baseline in IOP Secondary: Tear break-up time, mean Schirmer scores, assessment of safety	Primary: Both dorzolamide/timolol and brimonidine/timolol therapies were associated with comparable post-treatment IOPs (17.1 and 16.9 mm Hg, respectively; *P*=0.0000 for both). Dorzolamide/timolol and brimonidine/timolol were associated with comparable IOP-lowering effectiveness compared to baseline at the end of treatment (29.0 vs 31.3%; *P*=0.7363). Secondary: Dorzolamide/timolol and brimonidine/timolol were associated with comparable pre-treatment (*P*=0.1485) and post-treatment Schirmer scores (*P*=0.2314). Dorzolamide/timolol and brimonidine/timolol were associated with comparable pre-treatment mean tear break-up times (*P*=0.0506); however, the post-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment mean tear break-up times were significantly lower with dorzolamide/timolol (*P*=0.0397). Burning was significantly more frequent with dorzolamide/timolol than with brimonidine/timolol therapy (43 vs 19%; *P*=0.0182). Foreign body sensation was more common with dorzolamide/timolol than with brimonidine/timolol therapy; however, the difference was not statistically significant (28 vs 12%; *P*=0.0736). Other reported side effects were comparable between the two treatment groups (*P*>0.05) and included the following: conjunctival hyperemia (12 vs 14%), blurred vision (7 vs 5%), itching (12 vs 12%), secretion (7 vs 7%), dryness (7 vs 5%), blepharitis (5 vs 2%).
Konstas et al[35] Dorzolamide/timolol ophthalmic solution (Cosopt®) BID for 3 months, following 8 weeks of timolol 0.5% BID run-in period vs brimonidine/timolol ophthalmic solution (Combigan®) BID for 3 months, following 8 weeks of timolol 0.5% BID run-in period	PRO, XO Patients between the ages of 39 and 85, early-to-moderate primary open-angle glaucoma, best-corrected long-distance Snellen visual acuity greater than 0.1 in the study eye, open anterior chamber angles, untreated baseline IOP greater than 25 mm Hg and lower than 40 mm Hg at 1,000 (±1 hour)	N=77 (one eye for each patient) 8 months (2 months mono-therapy, 3 months combination treatment periods)	Primary: Mean 24-hour change in IOP from baseline Secondary: Assessment of safety	Primary: The mean 24-hour IOP was significantly reduced with both dorzolamide/timolol and brimonidine/timolol therapies compared to timolol monotherapy (*P*<0.001). Dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mm Hg; *P*<0.001). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol (*P*=0.03 and *P*=0.012, respectively). Secondary: Patients receiving dorzolamide/timolol experienced bitter taste (18.3%) and stinging (16.7%) more often than when treated with brimonidine/timolol (*P*=0.001 and *P*=0.012, respectively). Conjunctival hyperemia was more frequently reported in association with brimonidine/timolol compared to dorzolamide/timolol therapy (16.7 vs 5%; *P*=0.039).
Garcia-Feijoo et al[36] Dorzolamide/timolol ophthalmic solution (Cosopt®) BID for 6 weeks, following 6 weeks of timolol 0.5% BID run-in period	PRO, R, XO Patients diagnosed with primary open-angle glaucoma	N=20 18 weeks (6 week timolol monotherapy phase; two 6 week	Primary: Mean change in diurnal IOP from baseline at six weeks (IOP was measured at nine hours [pre-instillation], 12	Primary: After six weeks, mean diurnal IOP was 16.28 mm Hg following brimonidine/timolol therapy and 17.23 mm Hg following dorzolamide/timolol therapy (difference, 0.95 mm Hg; *P*=0.03). Mean IOP at nine hours was 20.95 mm Hg at baseline. The baseline IOP was reduced to 15.85 mm Hg following brimonidine/timolol and 17.55 mm Hg following dorzolamide/timolol (difference, 1.70 mm Hg; *P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs brimonidine tartrate/ timolol maleate ophthalmic solution (Combigan®) BID for 6 weeks, following 6 weeks of timolol 0.5% BID run-in period		combination treatment phases)	hours, and 16 hours) Secondary: Percentage of patients with IOP<18 mm Hg at six weeks, assessment of safety	Mean IOP changes from baseline at 12 and 16 hours were comparable between the brimonidine/timolol and dorzolamide/timolol therapy groups (*P* value not reported). Secondary: Percentages of patients achieving a goal IOP <18 mm Hg were 85% following brimonidine/timolol compared to 60% of patients receiving dorzolamide/timolol therapy (*P*>0.05). There were no treatment-related adverse events reported with either therapy.
Shedden et al[24] Dorzolamide/timolol preservative-free ophthalmic solution BID vs dorzolamide/timolol preservative-containing ophthalmic solution BID	DB, PG, RCT Patients 21 year of age or older with bilateral open-angle glaucoma or intraocular hypertension as confirmed by an IOP ≥22 mm Hg	N=254 12 weeks	Primary: Change from baseline in trough IOP at week 12 Secondary: Change from baseline in trough IOP at other time points (weeks two and six), change from baseline in peak IOP at all time points	Primary: Treatment with dorzolamide/timolol preservative-free and preservative-containing formulations were found to be clinically equivalent with an estimated difference of 0.31 mm Hg between treatments for the change from baseline in trough IOP at week 12. Secondary: At all drug trough and peak time points during the study (weeks two, six and 12), the estimated difference between the study groups in terms of change in IOP from baseline was less than 0.5 mm Hg. The mean change in trough IOP was 12.3% for the preservative-free group compared to 11.0% for the preservative-containing treatment group. The mean change in peak IOP at week 12 was 14.0% for the preservative-free group compared to 14.3% in the preservative-containing treatment group.
Martinez et al[37] Dorzolamide 2% BID, in addition to timolol 0.5% bid for 5 years vs brinzolamide 1% BID, in addition to timolol 0.5% bid for 5 years	PG, PRO, R Patients 40 years of age and older, diagnosed with primary open-angle glaucoma, with a mean diurnal IOP ≥20 mm Hg under treatment with beta-blockers (for ≥6	N=161 60 months	Primary: Change from baseline in IOP, percentage of patient eyes achieving IOP <18 mm Hg, systemic blood pressure, ocular perfusion pressure, end-diastolic velocity,	Primary: At study endpoint, the mean percentage of IOP reduction from baseline was 20.3% (*P*<0.0001) in the dorzolamide/timolol group and 21% (*P*<0.0001) in the brimonidine/timolol group. The difference between the two groups in IOP reduction from baseline was not statistically significant (*P*=0.159). Mean IOP at the end of the study was <18 mm Hg in 42% of eyes in the dorzolamide/timolol group and 47% of eyes in the brimonidine/timolol group (*P*=0.583). There were no significant changes in systemic blood pressure in either of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Timolol 0.5% was administered as one drop in each eye BID during the 4-week, run-in period, in each of the two treatment groups.	months) as monotherapy, mean diurnal IOP ≥20 mm Hg under treatment with timolol 0.5% BID as monotherapy, early visual field defect, visual acuity ≥0.3 and an equivalent spherical refractive error between +3.00 D and -6.00 D		resistivity index, visual field progression risk Secondary: Not reported	two treatment groups (*P*>0.05). Ocular perfusion pressure increased significantly in both treatment groups (*P*<0.0001). At study endpoint, end-diastolic velocity values in all retrobulbar vessels were significantly lower in the brimonidine/timolol group than in the dorzolamide/timolol group (*P*<0.001). At study endpoint, mean resistivity index was significantly higher in the brimonidine/timolol group than in the dorzolamide/timolol group in all retrobulbar vessels (*P*<0.0001). In a multivariate analysis, progression risk was significantly lower in eyes treated with dorzolamide/timolol compared to patients treated with brimonidine/timolol (HR, 0.65; 95%CI, 0.41 to 0.90). Secondary: Not reported
Renieri et al[25] Dorzolamide/timolol (Cosopt-S®) preservative free BID administered for 12 weeks	MC, OL, PRO Patients diagnosed with glaucoma and requiring IOP reduction, intolerant to benzalkonium chloride or active agents of previously used eye drops	N=2,298 12 weeks	Primary: IOP reduction from baseline at 12 weeks Secondary: Proportion of patients with IOP ≤21 mm Hg, adverse events	Primary: At 12 weeks, patients exhibited a mean absolute reduction from baseline in IOP of 4.1 mm Hg (-17.3%; *P* value not reported). Secondary: The proportion of patients with IOP ≤21 mm Hg increased from 59.9% at baseline to 94.6% after 12 weeks (*P* value not reported). The most frequently reported adverse events were burning eyes (2.4%) and ocular hyperemia (0.9%). Local tolerability improved in 79.3% of patients who switched to the preservative-free dorzolamide/timolol formulation from other anti-glaucoma therapy. The strongest improvement in local tolerability was noted in patients who had earlier received bimatoprost (97.7%) and brimonidine (93.9%). Furthermore, 84.6 and 84.0% of patients previously receiving brimonidine/timolol and dorzolamide/timolol products, respectively, experienced improvement of local tolerability after switching to the preservative-free dorzolamide/timolol.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Konstas et al[18] Latanoprost 0.005% 1 drop in the affected eye(s) QPM and placebo 1 drop in the affected eye(s) QAM vs dorzolamide/timolol 2%/0.5% 1 drop in the affected eye(s) BID	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 6 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, 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 (mm Hg±SD) 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: At month two, 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) than the latanoprost group. Latanoprost was associated with higher rates of hypertrichosis (*P*=0.02), headache (*P*=0.04) and ocular itching (*P*=0.004).
Sonty et al[19] Dorzolamide/timolol 2%/0.5% one drop in the affected eye(s) BID vs latanoprost 0.005% one drop in the affected eye(s) QPM	OL, PRO, XO Patients ages 18 years of age and older, with a clinical diagnosis of primary open angle glaucoma, pigment-dispersion or exfoliation glaucoma, or ocular hypertension, IOP ≤31 mm Hg in both eyes, IOP 19 to 31 mm Hg in at least one eye, a	N=59 12 weeks	Primary: Reduction in IOP Secondary: Change in overall performance, typical daily activities, limitations of activities, compliance, satisfaction or quality of life as evaluated by the	Primary: At visit one patients previously insufficiently controlled on latanoprost had a mean IOP of 22.2±2.4 mm Hg at eight hours and 21.4±2.5 mm Hg at 10 hours. At visit one, patients taking dorzolamide/timolol had a mean IOP of 18.3±2.6 mm Hg at 10 hours, and at visit two which occurred at week four, and a mean IOP of 19.8±3.8 mm Hg at eight hours and 17.9±3.5 mm Hg at 10 hours at visit three which occurred at week 12. After switching from latanoprost to dorzolamide/timolol the mean decrease at 8 hours was -2.4±3.3 mm Hg and at 10 hours was -3.5±3.3 mm Hg (*P*<0.0001 for both). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	visual acuity of at least 20/200 in each eye, and previous treatment with latanoprost dosed QPM for at least four consecutive weeks		Comparison of Ophthalmic Medications for Tolerability Questionnaire, and adverse events	No difference was seen between the two treatments with regards to overall performance, typical daily activities, limitations of activities, compliance, satisfaction or quality of life (*P*>0.05 for all). A greater number of patients were found to have a higher frequency in burning and/or stinging and bitter taste when treated with dorzolamide/timolol (*P*>0.0001 for both), while unusual taste and itchy eyes were found to be associated with latanoprost (*P*=0.02 and *P*=0.05 respectively). The most common adverse events reported by patients treated with dorzolamide/timolol were burning upon instillation and ocular hyperemia (*P* value not reported).
Fechtner et al[20] Dorzolamide/timolol 2%/0.5% 1 drop into both eye(s) BID vs latanoprost 0.005% 1 drop into both eyes QD	2 DB, MC, PG, RCT Patients ≥18 years of age diagnosed with bilateral open angle glaucoma or ocular hypertension	Study 1 N=256 Study 2 N=288 3 months	Primary: Mean change from baseline in daytime diurnal IOP Secondary: Assessment of safety and tolerability	Primary: Study 1: Both treatment groups reduced IOP between 25 to 30%. When the groups were compared at three months, the mean reduction in IOP was -0.44 mm Hg greater with dorzolamide/timolol than latanoprost (CI, -0.85 to 0.77). Study 2: Both treatment groups reduced IOP between 25 to 30%. When the groups were compared at 3 months, the mean reduction in IOP was -0.57 mm Hg greater with dorzolamide/timolol than latanoprost (CI, -1.31 to 0.16). Secondary: Study 1: Adverse events that occurred with both groups were mild to moderate and localized to the eye. The most common adverse events seen with both medications were ocular stinging, ocular itching, blurred vision, conjunctival hyperemia and taste perversion. The two most common adverse events in the study were ocular stinging (23 vs 7%) and taste perversion (10 vs 2%) which occurred significantly more in the dorzolamide/timolol group vs the latanoprost group (*P*<0.05). Study 2: Adverse events that occurred with both groups were mild to moderate and localized to the eye. The most common adverse events seen with both medications were ocular stinging, ocular itching, blurred vision, conjunctival

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				hyperemia and taste perversion. The most common adverse event in the study was ocular stinging (10 vs 2%) which occurred significantly more in the dorzolamide/timolol group vs the latanoprost group (*P*<0.05). Taste perversion occurred in only 2% of the time in the dorzolamide/timolol group and was not present in the latanoprost group; however, the results were not significant (*P* value not reported).
Nguyen et al[22] Dorzolamide/timolol 2%/0.5% and a prostaglandin analogue vs dorzolamide/timolol 2%/0.5% and brimonidine 0.2% and a prostaglandin analogue	OL, PRO Patients diagnosed with any type of glaucoma, on a regimen of either dorzolamide/timolol and a prostaglandin analogue, or dorzolamide/timolol, brimonidine (0.15 or 0.2% and a prostaglandin analogue	N=60 3 months	Primary: Change in IOP from baseline Secondary: Not reported	Primary: The baseline mean IOP in patients treated with dorzolamide/timolol and a prostaglandin analogue was 15.9 mm Hg. The mean IOP in these patients was significantly reduced at both one and three months after replacement of dorzolamide/timolol with timolol and brimonidine (*P*<0.001). Patients achieved a mean IOP of 13.3±0.9 mm Hg at month one and 13.0±1.0 mm Hg at month three. The mean change from baseline in IOP was -2.6 mm Hg, a 16.0% reduction, at month one and -2.6 mm Hg, a 16.4% reduction, at month three (*P*<0.001 for both). In patients treated with dorzolamide/timolol, brimonidine and a prostaglandin analogue the mean IOP was 15.9 mm Hg at baseline, 13.8 mm Hg at one month (*P*=0.053 vs baseline), and 13.8 at three months (*P*=0.079 vs baseline). The mean change from baseline IOP was found to be -2.1 mm Hg, a 9.5% reduction at month one, and -2.1 mm Hg, a 9.0% reduction at month three (*P* value not reported). Secondary: Not reported
Lesk et al[23] Dorzolamide/timolol 2%/0.5% one drop into affected eye(s) BID and latanoprost 0.005% one drop into affected eye(s) QD	MC, OL, PRO Patients 18 years of age and older, with a diagnosis of primary open angle glaucoma or ocular hypertension, who were previously	N=350 12 weeks	Primary: Reduction in IOP from baseline Secondary: Therapeutic response defined as a decrease >20% in IOP from	Primary: Both groups reported statistically significant changes in mean absolute and percent reductions in IOP at six and twelve weeks when compared to baseline (*P*<0.001). The changes in IOP between the groups at weeks six and twelve were not found to be statistically significant (*P* value not reported). Secondary: Therapeutic response rates >20% occurred after twelve weeks of treatment in 66.4% of the patients in the dorzolamide/timolol with latanoprost group and

<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>vs

dorzolamide/timolol 2%/0.5% one drop into affected eye(s) BID</td><td>treated with latanoprost monotherapy for four or more weeks but continued to have an IOP >21 mm Hg, deterioration of the visual fields regardless of IOP target, target IOP not achieved with latanoprost monotherapy, or an insufficient response in IOP reduction (<15% reduction) with latanoprost monotherapy</td><td></td><td>baseline and adverse events</td><td>52.9% of the patients in the dorzolamide/timolol group (P value not reported).

The most frequent adverse events reported for both groups were eye irritation and bad taste in the mouth (12.0 and 4.3%).</td></tr>
<tr><td>Clineschmidt et al[21]

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

vs

dorzolamide 2% 1 drop into affected eye(s) TID

vs

timolol 0.5% 1 drop into affected eye(s) BID</td><td>AC, DB, PG, RCT

Patients 21 years or older with diagnosis of bilateral open-angle glaucoma or ocular hypertension who had a day one IOP of 22 mm Hg after a 3-week run-in phase with timolol 0.5% BID</td><td>N=253

3 months</td><td>Primary:
Change from baseline in IOP at hour 0 and two after week two, and months one, two, three compared between the combination and each component group

Secondary:
Assessment of safety and tolerability</td><td>Primary:
Across all time periods, dorzolamide/timolol was more effective at reducing IOP from baseline than the single agents.
<table>
<tr><th colspan="5">Difference Between Change in IOP</th></tr>
<tr><th colspan="2">Examination</th><th>Treatment Group</th><th>Estimated Difference Between Means</th><th>95% CI</th></tr>
<tr><td rowspan="9">Hour 0</td><td rowspan="3">Week 2</td><td>Combination – dorzolamide</td><td>-4.04</td><td>-7.99 to -0.09</td></tr>
<tr><td>Combination – timolol</td><td>-5.48</td><td>-8.76 to -2.20</td></tr>
<tr><td>Dorzolamide - timolol</td><td>1.64</td><td>-2.34 to 5.61</td></tr>
<tr><td rowspan="3">Month 1</td><td>Combination – dorzolamide</td><td>-4.89</td><td>-9.03 to -0.76</td></tr>
<tr><td>Combination – timolol</td><td>-3.43</td><td>-6.84 to -0.02</td></tr>
<tr><td>Dorzolamide - timolol</td><td>-1.45</td><td>-5.61 to 2.71</td></tr>
<tr><td rowspan="2">Month 2</td><td>Combination – dorzolamide</td><td>-4.67</td><td>-9.08 to -0.25</td></tr>
<tr><td>Combination – timolol</td><td>-3.46</td><td>-7.10 to 0.18</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td rowspan="13">Hour 2</td><td rowspan="3">Month 3</td><td>Dorzolamide - timolol</td><td>-1.27</td><td>-5.72 to 3.17</td></tr>
<tr><td>Combination – dorzolamide</td><td>-5.63</td><td>-10.15 to -1.12</td></tr>
<tr><td>Combination – timolol</td><td>-3.91</td><td>-7.63 to -0.19</td></tr>
<tr><td rowspan="3">Week 2</td><td>Dorzolamide - timolol</td><td>-1.53</td><td>-6.07 to 3.01</td></tr>
<tr><td>Combination – dorzolamide</td><td>-4.72</td><td>-8.59 to -0.85</td></tr>
<tr><td>Combination – timolol</td><td>-7.74</td><td>-10.98 to -4.49</td></tr>
<tr><td rowspan="3">Month 1</td><td>Dorzolamide - timolol</td><td>3.24</td><td>-0.69 to 7.16</td></tr>
<tr><td>Combination – dorzolamide</td><td>-8.55</td><td>-13.25 to -3.86</td></tr>
<tr><td>Combination – timolol</td><td>-8.68</td><td>-12.59 to -4.77</td></tr>
<tr><td rowspan="3">Month 2</td><td>Dorzolamide - timolol</td><td>0.17</td><td>-4.60 to 4.94</td></tr>
<tr><td>Combination – dorzolamide</td><td>-3.92</td><td>-8.55 to 0.71</td></tr>
<tr><td>Combination – timolol</td><td>-7.51</td><td>-11.37 to -3.66</td></tr>
<tr><td rowspan="3">Month 3</td><td>Dorzolamide - timolol</td><td>3.87</td><td>-0.83 to 8.57</td></tr>
<tr><td>Combination – dorzolamide</td><td>-9.71</td><td>-14.78 to -4.64</td></tr>
<tr><td>Combination – timolol</td><td>-11.13</td><td>-15.35 to 6.90</td></tr>
<tr><td>Dorzolamide - timolol</td><td>1.25</td><td>-3.90 to 6.40</td></tr>
</table>

Secondary:
When the fixed dose combination was compared to the single agents, the combination showed significantly more adverse events than either single agent (combination, 63% vs timolol, 43%; P=0.007 and combination, 41% vs dorzolamide, 23%; P=0.007).

The most common adverse events were burning and/or stinging of the eyes which occurred significantly more in the combination than timolol when they were compared (30 vs 8%; P=0.001) but, the difference between the fixed dose combination and dorzolamide was not significantly different (30 vs 24%; P not reported).</td></tr>
<tr><td>Cheng et al[28]

Latanoprost 0.005% 1</td><td>MA of 14 RCT’s

Patients with</td><td>N=2,149

Duration</td><td>Primary:
Reduction from baseline to</td><td>Primary:
Changes in mean reduction in IOP were comparable at one, two, three, and six months between latanoprost and dorzolamide/timolol therapy. At one month, the</td></tr>
</table>

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%-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	endpoint in diurnal mean IOP Secondary: Reduction from baseline to endpoint in IOP at 10 AM within a range of ±1 hour	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 (pooled RR, 0.96; 95% CI, 0.21 to 4.46; *P*=0.96). Latanoprost was associated with higher rates of conjunctival hyperemia compared to dorzolamide/timolol therapy (6.2% vs 2.5%; RR, 2.38; 95% CI, 1.47 to 3.83; *P*=0.0004). Latanoprost was associated with higher rates of iris pigmentation compared to 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 withdrawal rates due to adverse events compared to latanoprost (4.0% vs 1.2%; RR, 0.34; 95% CI, 0.13 to 0.84; *P*=0.02). Dorzolamide/timolol 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;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.00001).
Webers et al[29] 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%/0.5% BID All patients had to complete a run-in phase of at least 2 weeks on timolol 0.5% BID monotherapy.	MA of 17 RCT's Over 85% of patients diagnosed with open-angle glaucoma or ocular hypertension	N=4,059 Duration varied from 1 to 3 months	Primary: Pooled change from baseline in IOP Secondary: Not reported	Primary: The absolute pooled mean change for dorzolamide/timolol, irrespective of concomitant or fixed, from baseline was -3.9 mm Hg (95% CI, -4.2 to -3.6) and -4.9 (95% CI, -5.2 to -4.6) at trough and peak, respectively. The relative change in IOP was -15.7% (95% CI, -17.2 to -14.3) and -20.1% (95% CI, -21.1 to -19.2) at trough and peak, respectively. Values for latanoprost were separated into concomitant and fixed use groups. The concomitant use of latanoprost and timolol gave an absolute pooled mean change from baseline of -6.0 (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 (95% CI, -3.8 to -2.2) and relative change of -13.4% (95% CI, -16.0 to -10.8). Secondary: Not reported

*Not available in the United States.
Study abbreviations: AC=active control, BID=twice daily, CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PG=parallel-group, PRO=prospective, QAM=every morning, QD=once a day, QPM=every evening, SB=single blind, R=randomized, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, TID=three times daily, XO=crossover
Miscellaneous abbreviations: IOP=intraocular pressure

Special Populations

Table 5. Special Populations[8-11]

Generic Name	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Brimonidine/ timolol maleate	Dosage adjustment not required in the elderly. Effectiveness and safety in pediatric patients <2 years of age have not been established.	Effectiveness and safety in patients with renal impairment have not been evaluated in clinical trials.	Effectiveness and safety in patients with hepatic impairment have not been evaluated in clinical trials.	C	Yes† (% not reported). Use with caution.
Brinzolamide/ brimonidine	Dosage adjustment not required in the elderly. Contraindicated in children <2 years of age.	Not recommended in patients with a creatinine clearance <30 mL/minute.*	Use with caution.*	C	Unknown. Use with caution.
Dorzolamide/ timolol maleate	Dosage adjustment not required in the elderly. Effectiveness and safety in pediatric patients <2 years of age have not been established.	Not recommended in patients with a creatinine clearance <30 mL/minute.*	Use with caution.*	C	Yes† (% not reported). Use with caution.
Dorzolamide/ timolol maleate PF	Dosage adjustment not required in the elderly. Effectiveness and safety in pediatric patients <2 years of age have not been established.	Not recommended in patients with a creatinine clearance <30 mL/minute.*	Use with caution.*	C	Yes† (% not reported). Use with caution.

*No adequate controlled clinical trials.
†Timolol maleate.

Adverse Events

Table 6. Adverse Events (%)[8-11]

Adverse Event(s)	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
Cardiovascular				
Arrhythmia	✔	-	✔	✔
Bradycardia	✔	✔	<1	<1

Adverse Event(s)	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
Cardiac arrest	✔	-	✔	✔
Cardiac failure	✔	-	<1	<1
Cerebral ischemia	✔	-	✔	✔
Cerebral vascular accident	✔	-	<1	<1
Chest pain	✔	<1	<1	<1
Claudication	✔	-	✔	✔
Cold hands and feet	✔	-	✔	✔
Edema	✔	-	✔	✔
Heart block	✔	-	<1	<1
Hypertension	1 to 5	-	1 to 5	1 to 5
Hypotension	✔	-	<1	<1
Myocardial infarction	-	-	<1	<1
Palpitation	✔	-	✔	✔
Pulmonary edema	✔	-	✔	✔
Reynaud's phenomenon	✔	-	✔	✔
Syncope	✔	-	✔	✔
Tachycardia	✔	✔	-	-
Worsening of angina pectoris	✔	-	✔	✔
Central Nervous System				
Anxiety	✔	-	✔	✔
Confusion	✔	-	✔	✔
Depression	1 to 5	-	<1	<1
Disorientation	✔	-	✔	✔
Dizziness	✔	<1	1 to 5	1 to 5
Hallucinations	✔	-	✔	✔
Headache	1 to 5	1 to 5	1 to 5	1 to 5
Itching	✔		-	-
Increase signs and symptoms of myasthenia gravis	✔	-	✔	✔
Insomnia	✔	-	✔	✔
Memory loss	✔	-	✔	✔
Nervousness	✔	-	✔	✔
Nightmares	✔	-	✔	✔
Paresthesia	✔	-	<1	<1
Somnolence	1 to 5	-	✔	✔
Dermatologic				
Alopecia	✔	<1	✔	✔
Contact dermatitis	-	-	✔	✔
Dermatitis	-	1 to 5	-	-
Epistaxis	-	-	✔	✔
Erythema	✔	-	-	-
Exacerbation of psoriasis	✔	-	✔	✔
Psoriasiform rash	✔	-	✔	✔
Rash	✔	-	<1	<1
Rhinitis	✔	1 to 5	-	-
Vasodilation	✔	-	-	-
Endocrine and Metabolic				
Edema	✔	-	-	-
Masked symptoms of hypoglycemia in insulin-	✔	-	✔	✔

Adverse Event(s)	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
dependent diabetes				
Gastrointestinal				
Anorexia	✔	-	✔	✔
Diarrhea	✔	<1	<1	<1
Dry mouth	1 to 5	3 to 5	<1	<1
Dyspepsia	✔	<1	1 to 5	1 to 5
Nausea	✔	<1	1 to 5	1 to 5
Vomiting	-	-	<1	<1
Hypersensitivity				
Allergic reactions	-	<1	-	-
Anaphylaxis	✔	-	✔	✔
Angioedema	✔	-	✔	✔
Bronchospasm	-	-	✔	✔
Localized and generalized rash	✔	-	✔	✔
Palpebral reaction	-	-	✔	✔
Pruritus	-	-	✔	✔
Urticaria	✔	<1	✔	✔
Ocular				
Allergic conjunctivitis	5 to 15	3 to 5	-	-
Blepharitis	1 to 5	1 to 5	1 to 5	1 to 5
Blepharoconjunctivitis	✔	-	-	-
Blurred vision	✔	3 to 5	5 to 15	5 to 15
Cataract	✔	-	-	-
Choroidal detachment following filtration surgery	✔	-	<1	<1
Cloudy vision	-	-	1 to 5	1 to 5
Conjunctival discharge	-	-	1 to 5	1 to 5
Conjunctival edema	✔	-	1 to 5	1 to 5
Conjunctival erythema	✔	-	-	-
Conjunctival folliculosis	5 to 15	-	1 to 5	1 to 5
Conjunctival hemorrhage	✔	-	-	-
Conjunctival hyperemia	5 to 15	-	5 to 15	5 to 15
Conjunctival injection	-	-	1 to 5	1 to 5
Conjunctivitis	✔	<1	1 to 5	1 to 5
Corneal erosion	1 to 5	-	1 to 5	1 to 5
Corneal punctate staining	-	-	1 to 5	1 to 5
Cortical lens opacity	-	-	1 to 5	1 to 5
Cystoid macular edema	✔	-	✔	✔
Decreased corneal sensitivity	✔	-	✔	✔
Diplopia	✔	<1	✔	✔
Discharge	1 to 5	-	-	-
Dry eye	1 to 5	1 to 5	-	-
Elevation in intraocular pressure	-	-	✔	✔
Epiphora	1 to 5	-	-	-
Eye crusting	-	-	✔	✔
Eye debris	-	-	1 to 5	1 to 5
Eye discomfort	-	-	1 to 5	1 to 5
Eye fatigue	-	<1	-	-
Eye irritation	1 to 5	3 to 5	-	-
Eye pain	1 to 5	-	1 to 5	1 to 5

Adverse Event(s)	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
Eye pruritus	5 to 15	-	-	-
Eyelid edema	1 to 5	-	1 to 5	1 to 5
Eyelid erythema	1 to 5	-	1 to 5	1 to 5
Eyelid exudates/scales	-	-	1 to 5	1 to 5
Eyelid pruritus	1 to 5	-	-	-
Follicular conjunctivitis	✔	-	-	-
Foreign body sensation	1 to 5	1 to 5	1 to 5	1 to 5
Glaucomatous cupping	-	-	1 to 5	1 to 5
Iridocyclitis	-	-	<1	<1
Iritis	✔	-	-	-
Irritation upon instillation	✔	-	-	-
Keratitis	✔	-	-	-
Keratoconjunctivitis sicca	✔	<1	-	-
Keratopathy	-	<1	-	-
Lens nucleus coloration	-	-	1 to 5	1 to 5
Lens opacity	-	-	1 to 5	1 to 5
Lid margin crusting/sticky sensation	-	<1	-	-
Miosis	✔	-	-	-
Nuclear lens opacity	-	-	1 to 5	1 to 5
Ocular allergic reaction	✔	-	-	-
Ocular burning	5 to 15	-	30	30
Ocular discharge	-	1 to 5	1 to 5	1 to 5
Ocular discomfort	-	1 to 5	-	-
Ocular dryness	-	-	1 to 5	1 to 5
Ocular hyperemia	-	1 to 5	-	-
Ocular itching	-	1 to 5	5 to 15	5 to 15
Ocular keratitis	-	1 to 5	-	-
Ocular pain	-	1 to 5	1 to 5	1 to 5
Photophobia	✔	-	<1	<1
Post-subcapsular cataract	-	-	1 to 5	1 to 5
Pseudopemphigoid	✔	-	✔	✔
Ptosis	✔	-	✔	✔
Refractive changes	✔	-	-	-
Signs and symptoms of ocular allergic reaction	-	-	✔	✔
Stinging	5 to 15	-	30	30
Stinging upon instillation	-	-	-	-
Superficial punctate keratitis	1 to 5	-	5 to 15	5 to 15
Tearing	✔	<1	1 to 5	1 to 5
Tinnitus	✔	-	✔	✔
Visual disturbance	1 to 5	-	✔	✔
Visual field defect	✔	-	1 to 5	1 to 5
Vitreous detachment	✔	-	1 to 5	1 to 5
Vitreous floaters	✔	-	-	-
Worsened visual acuity	✔	-	-	-
Respiratory				
Apnea	✔	-	-	-
Bronchitis	✔	-	1 to 5	1 to 5
Bronchospasm	✔	-	✔	✔

Adverse Event(s)	Brimonidine/ Timolol Maleate	Brinzolamide/ Brimonidine	Dorzolamide/ Timolol Maleate	Dorzolamide/ Timolol Maleate PF
Coughing	✔	-	1 to 5	1 to 5
Dyspnea	✔	<1	<1	<1
Nasal congestion	✔	-	-	-
Nasal dryness	✔	-	-	-
Pharyngitis	✔	<1	1 to 5	1 to 5
Respiratory failure	✔	-	<1	<1
Respiratory infection	✔	-	-	-
Sinus infection	✔	-	-	-
Sinusitis	✔	-	1 to 5	1 to 5
Upper respiratory infection	-	-	1 to 5	1 to 5
Urogenital				
Decreased libido	✔	-	✔	✔
Impotence	✔	-	✔	✔
Peyronie's disease	✔	-	✔	✔
Retroperitoneal fibrosis	✔	-	✔	✔
Other				
Abdominal pain	-	-	1 to 5	1 to 5
Abnormal taste	✔	-	-	-
Allergic reactions	✔	-	-	-
Allergic sensitizations	-	-	✔	✔
Anaphylaxis	✔	-	-	-
Asthenia	1 to 5	-	✔	✔
Back pain	-	-	1 to 5	1 to 5
Fatigue	✔	-	✔	✔
Flu syndrome	✔	-	-	-
Hypercholesterolemia	✔	-	-	-
Hypothermia	✔	-	-	-
Hypotonia	✔	<1	-	-
Influenza	-	-	1 to 5	1 to 5
Kidney pain	-	<1	-	-
Secondary infections	-	-	✔	✔
Swelling	✔	-	-	-
Systemic lupus erythematosus	✔	-	✔	✔
Taste perversion	✔	3 to 5	30	30
Urinary tract infection	-	-	1 to 5	1 to 5
Urolithiasis	-	-	<1	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications/Precautions

Brimonidine/timolol maleate, dorzolamide/timolol maleate and dorzolamide/timolol maleate PF are contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of the product.[8-11] Brinzolamide/brimonidine is contraindicated in patients with hypersensitivity to any component of the product and in neonates and infants under the age of two years.[11]

Due to the potential systemic absorption of the ophthalmic glaucoma combination agents, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration.[8-11] Severe adverse reactions may include respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma,

and rarely death associated with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate. Fatalities have occurred rarely due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration.[8-11]

Brimonidine/timolol maleate may potentiate syndromes associated with vascular insufficiency therefore should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.[8] Brinzolamide/brimonidine, dorzolamide/timolol maleate and dorzolamide/timolol maleate PF have not been evaluated in patients with acute-angle glaucoma.[9-11] Additionally, brinzolamide/brimonidine, dorzolamide/timolol maleate and dorzolamide/timolol maleate PF should be used with caution in patients with low endothelial cell counts due to an increased potential for developing corneal edema.

Beta-adrenergic receptor blockade may precipitate more severe cardiac failure and sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractivity.[8-11] In patients without a previous history of cardiac history continued depression of the myocardium with beta-adrenergic blocking agents over a period of time can, in some cases, lead to cardiac failure. The ophthalmic glaucoma combination agents should be discontinued at the first signs and symptoms of cardiac failure.

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial.[8-11] Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients who are receiving insulin or oral hypoglycemic agents. Additionally, beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia and certain clinical signs of hyperthyroidism.

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms, and timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.[8-11]

Drug Interactions

Table 7. Drug Interactions[8-11,38]

Generic Name	Interacting Medication or Disease	Potential Result
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, dorzolamide/timolol maleate, dorzolamide/timolol maleate PF)	Beta-adrenergic blocking agents	The potential additive effect either on intraocular pressure or on the known systemic effects of beta blockage should be observed. The concomitant use of two ophthalmic beta-adrenergic blocking agents is not recommended.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, dorzolamide/timolol maleate, dorzolamide/timolol maleate PF)	Calcium antagonists and digitalis	Patients should be monitored for possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, simultaneous use should be avoided.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, dorzolamide/timolol maleate, dorzolamide/timolol maleate PF)	Catecholamine-depleting drugs (reserpine)	Possible additive effects and the production of hypotension and/or bradycardia which may result in vertigo, syncope, or postural hypotension. Close observation is required.

Generic Name	Interacting Medication or Disease	Potential Result
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, dorzolamide/timolol maleate, dorzolamide/timolol maleate PF)	CYP2D6 inhibitors (quinidine, selective serotonin reuptake inhibitors)	Potentiated systemic beta-blockade (decreased heart rate, depression) has been reported during combined treatment. CYP2D6 inhibitors inhibit the metabolism of timolol maleate.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, brinzolamide/brimonidine)	Antihypertensive/ cardiac glycosides	Brimonidine/ timolol maleate may reduce blood pressure.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, brinzolamide/brimonidine)	Central nervous system depressants (alcohol, anesthetic, barbiturate, opiate, or sedative)	The possibility of an additive or potentiating effect with central nervous system depressants should be considered.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, brinzolamide/brimonidine)	Monoamine oxidase inhibitors (MAOIs)	MAOIs may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension.
Ophthalmic glaucoma combinations (brimonidine/ timolol maleate, brinzolamide/brimonidine)	Tricyclic antidepressants	Tricyclic antidepressants can affect the metabolism and uptake of circulating amines.
Ophthalmic glaucoma combinations (brinzolamide/brimonidine, dorzolamide/ timolol maleate, dorzolamide/timolol maleate PF)	Acid- base disturbances	Although acid-base and electrolyte disturbances were not reported in clinical trials, these disturbances have been reported with oral carbonic anhydrase inhibitors and have resulted in drug interactions (toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving brinzolamide/brimonidine or dorzolamide/ timolol maleate.
Ophthalmic glaucoma combinations (brinzolamide/brimonidine, dorzolamide/ timolol maleate, dorzolamide/timolol maleate PF)	Carbonic anhydrase inhibitors	The potential exists for an additive effect on the known systemic effects of carbonic anhydrase inhibition. The concomitant administration of these two agents is not recommended.

Dosage and Administration

Table 8. Dosing and Administration[8-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Brimonidine/ timolol maleate	Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled intraocular pressure: Ophthalmic solution: instill one drop twice daily approximately 12 hours apart	Effectiveness and safety in pediatric patients <2 years of age have not been established.	Ophthalmic solution: 0.2%/0.5% (5, 10 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
Brinzolamide/ brimonidine	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension: Ophthalmic solution: instill one drop into affected eye(s) three times daily	Contraindicated in children <2 years of age.	Ophthalmic solution: 1%/0.2% (10 mL)
Dorzolamide/ timolol maleate	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers: Ophthalmic solution: instill one drop into affected eye(s) twice daily	Effectiveness and safety in pediatric patients <2 years of age have not been established.	Ophthalmic solution: 2%/0.5% (10 mL)
Dorzolamide/ timolol maleate PF	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers: Ophthalmic solution: instill one drop into affected eye(s) twice daily	Effectiveness and safety in pediatric patients <2 years of age have not been established.	Ophthalmic solution: 2%/0.5% (0.2 mL single-use vials)

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Glaucoma Panel, Preferred Practice Patterns Committee. Primary Open-Angle Glaucoma (2010)**[3]	Medical management • Unless contraindicated, medical therapy is the most common initial intervention to lower intraocular pressure (IOP). • Medication choice may be influenced by potential cost, side effects and dosing schedules. • Patient adherence to therapy is enhanced by using eye drops with the fewest side effects as infrequently as necessary to achieve the target IOP. • If target IOP is not achieved by one medication, additional medications, combination therapies, or switching of treatments may be considered to reach the target IOP. • Ophthalmic formulations of β adrenergic antagonists and prostaglandin analogs are most frequently used to lower IOP. • Prostaglandin analogs are the most effective IOP-lowering drugs and can be considered as initial medical therapy unless cost, side effects or intolerance preclude their use. • Alpha$_2$-adrenergic agonists, ophthalmic and oral carbonic anhydrase inhibitors and parasympathomimetics are less frequently used. • If a drug fails to reduce IOP despite adherence to treatment, it should be replaced with an alternative agent until effective medical treatment is achieved. • If a single medication effectively reduces IOP but the target IOP has not been achieved, combination therapy or switching to an alternative medication should be considered. • Laser trabeculectomy is an alternative for patients who cannot or will not use medications reliably due to cost, memory problems, difficulty with instillation, or intolerance to the medication. • Filtering surgery is an alternative after medications and laser trabeculectomy. • Cyclodestructive surgery is reserved for patients with reduced visual acuity and patients who are poor candidates for incision surgery.

Clinical Guideline	Recommendations
American Optometric Association: **Clinical Practice Guidelines: Care of the Patient with Open-Angle Glaucoma (2010)**[39]	Treatment options • Glaucoma treatment begins with pharmacological intervention, proceeding to laser therapy and surgery when necessary. • Treatment of open-angle glaucoma includes the use of topical or orally administered agents to enhance aqueous outflow, reduce aqueous production or both. Prostaglandin analogs • Latanoprost 0.005% lowers IOP by up to 35% when administered once daily and is at least as effective as timolol maleate in lowering IOP. It has additive effects when administered with other agents. • Bimatoprost 0.03% has a similar effectiveness to latanoprost. It reduces IOP up to 33%. • Travoprost 0.004% has a similar effectiveness to latanoprost. It reduces IOP up to 33%. Travoprost may be more effective than other active agents in lowering IOP in African Americans. Epinephrine compounds • Epinephrine is not as effective as other drugs in lowering IOP and their use is relatively rare. • An epinephrine prodrug, dipivefrin, is available in a 0.1% concentration and is the drug of choice among epinephrine products. The lower concentration of dipivefrin is equivalent in effectiveness to a 1 to 2% concentration of epinephrine, has better penetration of the cornea and reduced side effects. Alpha$_2$-adrenergic agonists • Apraclonidine lowers IOP by 25% and prevents the acute spike in IOP that may occur after argon laser trabeculoplasty and other laser procedures. • Apraclonidine is also effective in minimizing IOP increases after cycloplegia in patients with glaucoma. • Apraclonidine 0.05% is as efficacious as 0.5% timolol used twice daily. It may also have additive effects with timolol in lowering IOP and may be valuable for patients resistant to further reduction in IOP. • Brimonidine is more selective than apraclonidine for alpha$_2$- receptors. Brimonidine 0.2% reduces IOP up to 27%, without tachyphylaxis. When used twice a day, it is more effective than betaxolol and similar to timolol. As monotherapy, brimonidine is less effective than prostaglandin analogs but additive with timolol and latanoprost and can be used as combination or replacement therapy. β adrenergic antagonists • Timolol, carteolol, levobunolol, metipranolol and betaxolol (suspension) are unique β adrenergic antagonist preparations for treating glaucoma. The doses of β adrenergic antagonists used in treating glaucoma range from 0.25 to 1.0%, and are dosed once or twice daily. • Betaxolol may cause fewer pulmonary and cardiovascular side effects, but is less effective at lowering IOP compared to timolol, carteolol, levobunolol, and metipranolol. Carbonic anhydrase inhibitors • Acetazolamide is available as an injection or sustained-release capsules.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>

This class lowers IOP by 20 to 40%, but they are poorly tolerated. The most effective doses are 500 mg of acetazolamide once or twice daily and 50 mg of methazolamide two to three times daily.
Dorzolamide hydrochloride lowers IOP by 3 to 5 mm Hg. As adjunctive therapy, dorzolamide is approximately equivalent to 2% pilocarpine in further lowering IOP.
Brinzolamide is equal to dorzolamide in IOP-lowering effects. Both have additive effects when used with timolol.

<u>Miotic agents</u>

Pilocarpine is the miotic drug most frequently in glaucoma in doses ranging from 1 to 4%; the duration of action is at least six hours.
Pilocarpine also is available in a 4% gel preparation.

<u>Combination treatment:</u>

Studies support the rationale for combining separate topical glaucoma medications into a single formulation to decrease the number of applications per day, thereby increasing compliance.
Results from clinical studies demonstrate that combination treatment is more effective in reducing IOP compared to monotherapy with either agent alone.

</td></tr>
<tr><td>National Institute for Clinical Excellence: Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension (2009)[4]</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 beta-blockers or ophthalmic prostaglandin analogues.
Ophthalmic carbonic anhydrase inhibitors and ophthalmic sympathomimetics should be considered second-line medication therapy.
Pharmacological treatment should be switched to another class (ophthalmic beta-blocker, ophthalmic carbonic anhydrase inhibitor, ophthalmic prostaglandin analogue or ophthalmic sympathomimetic) when:

Medication intolerance to current medication is experienced.
Target IOP reduction has not been achieved to reduce the risk of vision loss.

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 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>No treat-</td><td>No treat-</td><td>No treat-</td><td>Beta-blocker†</td><td>Prosta-glandin</td><td>Prosta-glandin</td><td>Prosta-glandin</td></tr>
</table>
</td></tr>
</table>

Clinical Guideline	Recommendations

	ment	ment	ment		analogue	analogue	ana-logue

*Age threshold is to guide healthcare providers if the patient's vision is currently normal and treatment is purely preventative. Once the patient has reached the threshold the health care providers should discussed the discontinuation of the medication with the patient. If the patient develops glaucoma treatment should continue.
†If beta-blockers are contraindicated offer a prostaglandin analogue.

- Patients should be referred to an ophthalmologist when target IOP reduction cannot be achieved.

Treatment of patients with open angle glaucoma

- Ophthalmic prostaglandin analogues should be offered to:
  - Patients newly diagnosed with early or moderate open-angle glaucoma at risk of significant vision loss.
  - 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.
  - Reported intolerance to current medication.
- Patients should be offered surgery along with medication if they are at risk for vision loss despite treatment.
- If a patient IOP has not lowered after surgery, the following should be considered:
  - Pharmacological treatment with ophthalmic agents (beta-blocker, carbonic anhydrase inhibitor, prostaglandin analogue, or sympathomimetic).
  - Further surgery with pharmacological augmentation.
  - 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 (beta-blocker, carbonic anhydrase inhibitor, prostaglandin analogue, or sympathomimetic).
  - Laser trabeculoplasty or cyclodiode laser treatment.

Conclusions

Treatment of glaucoma currently focuses on decreasing intraocular pressure (IOP) by one of three methods: laser therapy, surgery, or medical intervention.[1-4] Medical intervention includes five classes of ophthalmic agents used for the long-term management of glaucoma: alpha$_2$ adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics, and prostaglandin analogues.

In trials involving combination products it was found that the addition of ophthalmic timolol maleate to ophthalmic dorzolamide provided additional reductions in IOP and the use of the fixed dose combination did not cause significant differences in the reduction of IOP from baseline when compared to using the agents separately.[11,12] In a trial comparing ophthalmic dorzolamide/timolol maleate to the individual components it was found that the combination product was more effective at reducing IOP from baseline at all time periods over three months of treatment.[19] When ophthalmic dorzolamide/timolol maleate was compared to ophthalmic brimonidine/timolol maleate it was found that both groups significantly reduced IOP from baseline (P<0.001) and the difference between groups was not significant (P value not reported).[20,21]

Treatment with ophthalmic dorzolamide/timolol preservative-free and preservative-containing formulations have been shown in clinical trials to be clinically equivalent with an estimated difference of 0.31 mm Hg between the two formulations for the change from baseline in trough IOP at week 12.[24] Furthermore, a study evaluating treatment with ophthalmic dorzolamide/timolol preservative-free demonstrated a mean absolute reduction from baseline in IOP of 4.1 mm Hg.[25]

Treatment with fixed-dose ophthalmic brinzolamide/brimonidine has also been shown to be effective for the reduction of IOP. Two clinical trials comparing treatment with ophthalmic brinzolamide/brimonidine to monotherapy with the individual components have demonstrated a significantly greater reduction in IOP with combination therapy ($P<0.005$ for both).

Patients with a known hypersensitivity to beta adrenergic antagonists should use caution when using this class of medication.[8,9] Beta-adrenergic blocking agents should be used in caution in patients with diabetes mellitus, hyperthyroidism, and in patients with a diagnosis of asthma or severe chronic obstructive pulmonary disease. Cardiac effects such as effects on heart rate and blood pressure may occur with the use of beta-adrenergic blocking agents. Due to the potential for these effects, caution should be used in patients with a history of cardiac failure or heart block.

The use of the ophthalmic glaucoma combination agents are not specifically addressed in the current clinical guidelines; however, based on the Food and Drug Administration approved indications of these agents, it is likely that they will be used as second-line therapy in patients who did not achieve adequate results with first-line therapies.[8-11] The American Academy of Ophthalmology notes that ophthalmic formulations of beta adrenergic antagonists and prostaglandin analogs are recommended as first-line therapy for the treatment of increased IOP in patients with glaucoma.[3]

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