

WYOMING PDLAC THERAPEUTIC CLASS REVIEW

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OPHTHALMICS, GLAUCOMA AGENTS

This publication is a result of the collaboration of the Goold Health Systems, Inc. Clinical Workgroup and represents the opinion of these authors based on a review of the literature available at the time it was written. It is intended for the sole purpose of providing information to committee members in order to compare medications within a specified subset of clinical parameters. It is not intended to provide specific clinical advice for any condition, or to be an exhaustive review of all potential aspects of pharmacotherapies for any given condition. Medical evidence is rapidly changing, and no representation is made regarding the use of this material beyond the stated purpose.

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SYNOPSIS

Glaucoma is the second most common cause of permanent blindness in the United States and the most common cause of blindness among African-Americans. The prevalence of glaucoma in the United States in adults over 40 years old is estimated to be 1.86 percent.¹ As the American population ages, the prevalence is expected to rise. African-Americans have a higher prevalence compared to Caucasians; however, Caucasians have a steeper rise in open-angle glaucoma associated with advancing age.^{2,3} Generally, men are more frequently affected by glaucoma. Risk factors for the development of glaucoma include elevated IOP, advancing age, family history of glaucoma, African-American or Hispanic descent, and thinner central corneal thickness.⁴⁻⁶

Increased intraocular pressure (IOP) is common in glaucoma and is believed to contribute to the damage to the optic nerve which can lead to loss of visual sensitivity and field, but it is no longer considered a diagnostic criterion for glaucoma. Reduction of IOP may be accomplished by decreasing the rate of production of aqueous humor or increasing the rate of outflow of aqueous humor from the anterior chamber of the eye.⁷ Two major types of glaucoma have been identified: open-angle and closed-angle. Open-angle glaucoma accounts for the majority of cases. Ocular hypertension may precede glaucoma in some patients. Topical ocular hypotensive agents can delay or prevent the development of primary open-angle glaucoma in some patients.¹ In African-Americans with ocular hypertension, the use of topical ocular hypotensive agents has been shown to delay or prevent the onset of primary open-angle glaucoma.⁸

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

The drugs included in this therapeutic class review include: betaxolol (Betoptic®, Betoptic® S), bimatoprost (Lumigan®), brimonidine (Alphagan®, Alphagan P®), brimonidine/timolol (Combigan®), brinzolamide (Azopt®), carbachol (Carboptic®, Isopto Carbachol®), carteolol, dipivefrin (Propine®), dorzolamide (Trusopt®), dorzolamide/timolol (Cosopt®), echothiophate iodide (Phospholine Iodide®), latanoprost (Xalatan®), levobunolol (Betagan®), metipranolol (OptiPranolol®), pilocarpine (Isopto Carpine®, Pilopine HS®), timolol (Betimol®, Istalol®, Timoptic®, Timoptic-XE®), and travoprost (Travatan®, Travatan® Z).

FDA APPROVED INDICATIONS ⁵⁴⁻⁷²

The topical ophthalmic products within this review are indicated in the treatment of elevated intraocular pressure (IOP) in open-angle glaucoma. In addition to the treatment of open-angle glaucoma, pilocarpine is also indicated for the treatment of acute angle-closure glaucoma, while Combigan® is also indicated for the treatment of elevated IOP in those with glaucoma or ocular hypertension who require adjunctive or replacement therapy.

DOSAGE FORMS, DOSE, AND MANUFACTURER ⁵⁴⁻⁷²

Unless otherwise specified, dosing for ophthalmic drops includes instilling drops into the affected eye(s). In addition, dosing of drops will vary depending upon formulation used. With Phospholine Iodide® dosing, the strength can be increased for advanced disease or when there is resistance to other agents. The brand name for carteolol is Ocupress, but this is no longer manufactured.

Drug	Dosage Forms	Dose	Manufacturer
betaxolol (Betoptic S®)	<u>betaxolol Solution:</u> 0.5% <u>Betoptic® Suspension:</u> 0.25%	Soln: 1-2 drops BID Susp: 1 drop BID	Various generic manufacturers (Alcon Laboratories, Inc.)
bimatoprost (Lumigan®)	<u>Solution:</u> 0.03%	1 drop QPM	Allergan Inc.
brimonidine (Alphagan®) (Alphagan® P)	<u>Alphagan® Solution:</u> 0.2% <u>Alphagan® P Solution:</u> 0.1%, 0.15%	1 drop tid	Various generic manufacturers (Allergan, Inc.)
brimonidine/timolol (Combigan®)	<u>Solution:</u> 0.2%/0.5%	1 drop BID	Allergan Inc.
brinzolamide (Azopt®)	<u>Suspension:</u> 1%	1 drop TID	Alcon Laboratories, Inc.
carbachol (Isopto Carbachol®) (Carbotic®)	<u>Solution:</u> 0.75%, 1.5%, 2.25%, 3%	2 drops TID	Alcon Laboratories, Inc.
carteolol	<u>Solution:</u> 1%	1 drop BID	Generic manufactures
dipivefrin (Propine®)	<u>Solution:</u> 0.1%	1 drop BID	Various generic manufacturers (Allergan, Inc.)
dorzolamide (Trusopt®)	<u>Solution:</u> 2%	1 drop TID	Merck & Co., Inc.
dorzolamide/ timolol (Cosopt®)	<u>Solution:</u> 2/0.5%	1 drop BID	Merck & Co., Inc.
echothiophate iod. (Phospholine Iodide®)	<u>Solution for Reconstitution:</u> 0.03%, 0.06%, 0.125%, 0.25%	1 drop BID	Wyeth

Drug	Dosage Forms	Dose	Manufacturer
latanoprost (Xalatan®)	<u>Solution:</u> 0.005%	1 drop QPM	Pharmacia & Upjohn
levobunolol (Betagan®)	<u>Solution:</u> 0.25%, 0.5%	0.25% soln: 1-2 drops BID 0.5% soln: 1-2 drops QD-BID	Various generic manufacturers (Allergan, Inc)
metipranolol (Optipranolol®)	<u>Solution:</u> 0.3%	1 drop BID	Various generic manufacturers (Bausch & Lomb Inc.)
pilocarpine (Isopto Carpine®) (Pilopine HS®)	<u>Solution:</u> 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 8% <u>Pilocarpine HS® gel:</u> 4%	1-2 drops TID-QID, starting with 1 or 2% soln <u>Gel:</u> 0.5 inch ribbon in conjunctival sac QHS <u>Angle-closure glaucoma:</u> 1 drop q 5-6 min x 3-6. Then 1 drop q 1-3 h until normal pressure with 2% soln	Various generic manufacturers (Alcon Laboratories, Inc.)
timolol (Timoptic®) (Timoptic® XE) (Istalol®) (Betimol®)	<u>Solution:</u> 0.25%, 0.5% <u>Istalol Solution:</u> 0.5%	1 drop BID: once IOP maintained, may ↓ to 1 drop QD XE soln: 1 drop QD Istalol: 1 drop QAM	Various generic manufacturers (Merck & Co., Inc.) (Bausch & Lomb Inc.) (Santen)
travoprost (Travatan®) (Travatan Z®)	<u>Solution:</u> 0.004%	1 drop QPM	Alcon Laboratories, Inc.

PHARMACOLOGY ⁵⁴⁻⁷²

The glaucoma agents within this review all decrease IOP by different mechanisms. Beta blockers antagonize beta₁ and beta₂ adrenergic receptors therefore decreasing aqueous humor production. Carbonic anhydrase inhibitors decrease aqueous humor secretion. Parasympathomimetics are miotic agents that increase the outflow of aqueous humor. Prostaglandin analogs increase uveoscleral outflow without effects on aqueous flow. Sympathomimetics stimulate alpha₂-adrenergic receptors to decrease aqueous humor production and increase uveoscleral outflow.

The table below categorizes the mechanism of action of the glaucoma agents.

Ophthalmics, Glaucoma Agents-5

Drug	Beta Blocker	Carbonic Anhydrase Inhibitor	Para-sympathomimetic	Prostaglandin Analog	Sympathomimetic
betaxolol (Betoptic S®)	X				
bimatoprost (Lumigan®)				X	
brimonidine (Alphagan®) (Alphagan® P)					X
brimonidine/timolol (Combigan®)	X				X
brinzolamide (Azopt®)		X			
carbachol (Isopto carbachol®) (Carboptic®)			X		
carteolol	X				
dipivefrin (Propine®)					X
dorzolamide (Trusopt®)		X			
dorzolamide/ timolol (Cosopt®)	X	X			
echothiophate iod. (Phospholine Iod.®)			X		
latanoprost (Xalatan®)				X	
levobunolol (Betagan®)	X				
metipranolol (Optipranolol®)	X				
pilocarpine (Isopto Carpine®) (Pilopine HS®)			X		
timolol (Betimol®) (Istalol®) (Timoptic®)	X				

Drug	Beta Blocker	Carbonic Anhydrase Inhibitor	Para-sympathomimetic	Prostaglandin Analog	Sympathomimetic
travoprost (Travatan®) (Travatan Z®)				X	

PHARMACOKINETICS⁵⁴⁻⁷²

Ocular pigmentation may hinder penetration of pilocarpine. The lighter the pigmentation, the lower the strength needed and the darker the pigmentation the higher the strength needed. Combigan® showed slightly less lowering of IOP dosed twice daily vs using the combination of individual ingredients of timolol 0.5% twice daily and brimonidine 0.2% three times a day.

Drug	Onset	Duration	Peak Response	Other
betaxolol (Betoptic S®)	Within several hrs	After 2 weeks	12 to 24 hrs	
bimatoprost (Lumigan®)	4 hrs	N/A	8 to 12 hrs	If >1 OP drug being used, give 5 min apart
brimonidine (Alphagan®) (Alphagan® P)	N/A	12 hrs (with bid dosing)	2 hrs	If >1 OP drug being used, give 5 min apart <u>Alphagan P</u> : Benzalkonium chloride (BAK) free
brimonidine/timolol (Combigan®)	N/A	N/A	brim: 1-4 hrs tim: 1-3 hrs	If >1 OP drug being used, give 5 min apart
brinzolamide (Azopt®)	N/A	N/A	N/A	If >1 OP drug being used, give 10 min apart
carbachol (Isopto Carbachol®) (Carboptic®)	10-20 min	8 hrs	N/A	Carboptic® was discontinued in 2003
carteolol	N/A	8 hrs	2-3 hrs	
dipivefrin (Propine®)	30 min	N/A	1 hr	

Ophthalmics, Glaucoma Agents-7

Drug	Onset	Duration	Peak Response	Other
dorzolamide (Trusopt®)	N/A	8-12 hrs	2 hrs	If >1 OP drug being used, give 10 min apart
dorzolamide/ timolol (Cosopt®)	N/A	N/A	N/A	If >1 OP drug being used, give 10 min apart.
echothiophate iod. (Phospholine Iod.®)	N/A	N/A	N/A	Requires reconstitution. Keep refrigerated prior to reconstitution. After reconstitution, store at room temp up to 4 wks.
latanoprost (Xalatan®)	3-4 hrs	20-23 hrs	8-12 hrs	Store unopened bottle in refrigerator. Once open, room temp up to 6 wks.
levobunolol (Betagan®)	1 hr	24 hrs	2-6 hrs	Can be used with other anti-glaucoma agents
metipranolol (Optipranolol®)	30 min	24 hrs	2 hrs	Can be used with other anti-glaucoma agents
pilocarpine (Isopto Carpine®) (Pilopine HS®)	N/A	N/A	N/A	Ocular pigmentation may hinder penetration.
timolol (Timoptic®) (Timoptic® XE) (Istalol®) (Betimol®)	Istalol®: 30 min	XE & Istalol®: 24 hrs	Istalol®: 1-2 hrs	Give XE 10 min after others if >1 OP drug being used. Timoptic OcuDose is preservative free
travoprost (Travatan®) (Travatan Z®)	2 hrs	24 hrs	12 hrs	If >1 OP drug being used, give 5 min apart. Travatan Z in BAK free.

CLINICAL TRIALS

Clinical trials performed to obtain FDA approval confirmed all the medications in this therapeutic class to be superior in efficacy, as well as showing safety of the drug, when compared to placebo. The primary outcome measure used to assess efficacy of pharmacotherapy for glaucoma is the change in IOP as compared to baseline, expressed as an absolute value in mm Hg or as a relative percentage change from baseline. Timolol was the first beta-blocker marketed and is the gold standard to which other ophthalmic glaucoma agents are compared.

Meta-Analyses: A 2007 meta-analysis evaluated nine studies of the prostaglandin analogs for the management of glaucoma or ocular hypertension.⁵⁰ A total of 1,318 patients were evaluated in this analysis. Patients treated with travoprost and bimatoprost had lower IOP levels at the end of follow-up (-0.98 mmHg; $p=0.08$), and -1.04 mmHg lower than those treated with latanoprost ($p=0.06$). This analysis concluded that both travoprost and bimatoprost may be more effective in lowering IOP for patients with ocular hypertension or glaucoma.

In another meta-analysis completed in 2006, travoprost 0.004% was shown to have equivalent efficacy to bimatoprost and latanoprost in a total of 12 studies. In this analysis, travoprost was shown to have greater efficacy in reducing IOP than timolol.⁵¹

A larger, more comprehensive 2005 meta-analysis evaluated the IOP reduction of all commonly used glaucoma drugs.⁵² A total of 27 articles with 6,953 patients with trough IOP readings and 6,841 patients with peak IOP readings were included. Over 85 percent of patients had primary open-angle glaucoma or ocular hypertension. The greatest IOP reductions were reported with timolol, latanoprost, travoprost, and bimatoprost, with peak reductions of 27 to 33 percent and trough reductions of 26 to 29 percent from baseline.

A newer meta-analysis by Aptel et al⁷³ in 2008 included randomized controlled trials involving latanoprost, bimatoprost, and travoprost for assessment of their intraocular pressure (IOP) lowering effects, as well as tolerability. Eight trials met criteria for inclusion and included 1,610 patients. Results indicated that bimatoprost had the greatest IOP lowering change from baseline which was statistically significant when compared with latanoprost when assessed at all time points during the day (8am: $p=0.05$, noon: $p<0.001$, 4pm: $p=0.003$, 8pm: $p=0.040$), and when compared to travoprost for the daytime readings (8am: $p=0.004$, noon: $p=0.02$). Latanoprost and travoprost were equally efficacious in reducing IOP levels at all time points during the day ($p\leq 0.82$). Tolerability was based on the occurrence of conjunctival hyperemia. Although bimatoprost had the biggest IOP changes, it also had the greatest incidence of hyperemia compared to latanoprost and travoprost (latanoprost vs bimatoprost: $p<0.001$; travoprost vs bimatoprost: $p=0.05$).

A meta-analysis by Loon et al¹⁷ in 2007 included randomized controlled trials involving timolol compared with brimonidine for assessment of their intraocular pressure (IOP) reducing effects, as well as tolerability. Eight trials met criteria for inclusion, which included 2,387 subjects. Results indicated that there was not a statistically significant difference in IOP lowering between the two medications, while conclusions suggest that they are equally effective treatments for lowering IOP. Ocular allergy was reported more frequently with brimonidine as compared with timolol.

A systematic review by Hodge et al¹⁵ in 2008 surveyed randomized controlled trials involving latanoprost, brimonidine, and dorzolamide for assessment of their intraocular pressure (IOP) lowering effects, as well as tolerability. Eight trials met criteria for inclusion and included 1,722 patients. Results revealed that there was not a significant difference in the lowering of IOP with latanoprost use as compared to brimonidine use ($p=0.30$). Statistically significantly greater reductions of IOP were seen, however, with the latanoprost treatment group as compared to the dorzolamide group ($p<0.00001$). The brimonidine group reported more ocular adverse events compared with the latanoprost group ($p=0.0005$).

A number of multicenter, double-blind trials have been done to compare the safety, tolerability, and efficacy of bimatoprost 0.03% instilled once or twice daily with timolol 0.5% instilled twice daily in patients with ocular hypertension or glaucoma. Four studies reviewed found bimatoprost to be statistically superior to timolol in lowering IOP in patients with either ocular hypertension or glaucoma.^{31,32,33,34} Of the studies that compared the safety of bimatoprost, all studies showed it to be safe, with one study showing bimatoprost to have better ocular tolerability than timolol.³¹

A number of randomized, double-blind trials compared the safety, tolerability, and efficacy of travoprost with timolol in patients with open-angle glaucoma or ocular hypertension.^{42,43,44} Two of the three studies found travoprost to be statistically superior to timolol in reducing IOP, while the third study found travoprost to be either statistically superior or equal to timolol for reducing IOP. All trials found travoprost to be safe and tolerable.

Additional comparator trials are discussed in the table below.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Cantor et al ⁹ 2001	Multisite, double-masked, comparative clinical trial brimonidine 0.2% vs. betaxolol 0.25% suspension	N=159 4 weeks	Patients with glaucoma or ocular hypertension. 77.4% were white, 61.6% were female, and 56.0% had a diagnosis of open-angle glaucoma	-Compared clinical outcome and quality-of-life between two treatments. -Efficacy determined by IOP lowering effect from baseline.	-Mean IOP reductions after four weeks were -5.96 mm Hg with brimonidine and -5.07 mm Hg with betaxolol (p=NS). -More brimonidine (64.2%) patients achieved a reduction of greater than 20 percent in IOP than betaxolol patients (47.4%; p=0.033). -No serious adverse events were reported; however, more patients treated with betaxolol reported hyperemia (p=0.011). -Furthermore, the hyperemia reported with those taking betaxolol was significantly more severe (p=0.009).	-Although both treatments effectively lowered IOP from baseline after 4 weeks of treatment, the brimonidine treatment group was clinically successful in considerably more patients than betaxolol. -Brimonidine was better tolerated through the treatment period than betaxolol.
Whitson et al ¹⁰ 2004	Prospective, double-masked, randomized, crossover study brimonidine 0.2% vs. dorzolamide 2%	N=43 12 weeks	Patients diagnosed with open-angle glaucoma or ocular hypertension	-To compare the intraocular pressure (IOP) lowering effect of both treatments. -Change from baseline in IOP one and three hours after dosing was recorded	-The mean IOP reduction for both agents was -3 mm Hg (p=0.96) with reductions at hour one and hour three being similar for both agents (p=NS). -Although both treatments were well tolerated, dorzolamide was associated with more stinging (p=0.017) and burning (p<0.001) whereas brimonidine was	-Both brimonidine and dorzolamide were found to be comparable and equally effective for lowering IOP levels. -Both medications were well tolerated.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					associated with more dry eye complaints (p=0.04).	
Sharpe et al ¹¹ 2004	Randomized, double-blind, multicenter, prospective cross-over trial brimonidine 0.15% vs. dorzolamide 2%	N=33 8 weeks	Diagnosis of primary open angle glaucoma or ocular hypertension	-Compare the intraocular pressure (IOP) lowering effect between the two treatments. -IOP levels were measured at 8:00, 10:00, 18:00, and 20:00	-Reductions in IOP were similar between the two drugs. -The trough IOP for both agents after four weeks of therapy was 21 mm Hg for both treatments (p=0.90). -The mean diurnal IOP was 19.3 mm Hg for brimonidine (Alphagan® P) and 19.8 mm Hg for dorzolamide (p=0.46). - There was a tendency for brimonidine to have greater efficacy at the 10:00 measurement compared to dorzolamide. -More patients complained of stinging upon instillation with dorzolamide (p=0.02); otherwise, adverse effects were similar between the groups.	-Brimonidine and dorzolamide were found to have similar and comparable efficacy for treatment of lowering IOP associated with primary angle glaucoma or ocular hypertension.
Sall ¹² 2000	Randomized, multicenter, double-masked, prospective, parallel study	N=463	Patients diagnosed with open-angle glaucoma (with or without a pseudo-	-To compare intraocular pressure (IOP) lowering effects from baseline with the listed treatments.	-The mean IOP changes after 3 months of active therapy were 3.4 to 4.1 mmHg for brinzolamide BID, 4.1 to 4.8 mmHg for brinzolamide TID, and 4.3 to 4.9 mmHg for dorzolamide.	-Brinzolamide and dorzolamide were found to be clinically and statistically equivalent for treatment of lowering IOP associated with open-angle glaucoma or ocular

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	brinzolamide 1% TID vs. brinzolamide 1% BID vs dorzolamide 2% TID vs placebo	3 months	exfoliative or a pigmentary dispersion component) or ocular hypertension		<p>-All therapies were similar in efficacy in reducing IOP.</p> <p>-Burning and stinging upon dose instillation were significantly higher with dorzolamide (10.7%) compared to brinzolamide (3%).</p>	<p>hypertension.</p> <p>-Ocular comfort with instillation was higher with brinzolamide compared with dorzolamide.</p>
Mundorf et al ¹⁸ 2004	Multicenter, prospective, randomized, double-masked, parallel-group trial timolol 0.5% vs. timolol-LA (TLA) with potassium sorbate	N=332 1 year	<p>-Subjects ≥18 with open- angle glaucoma or ocular hypertension in 1 or both eyes and an un-medicated intraocular pressure (IOP) of ≥ 22mmHg</p> <p>-The baselines mean IOP was 25 mm Hg in both groups</p>	-The IOP on treatment difference at each visit	<p>-At all measurements of IOP, the two groups were similar with a mean post-treatment IOP of 18 to 19 mmHg at peak drug effect and 19 to 20 mmHg just prior to re-dosing.</p> <p>-Mean IOP reductions from baseline were 25.5-28.7% at peak and 20.8-24.7% at trough.</p> <p>-Burning and stinging on instillation, which was mostly described as mild, was reported by 41.6% in the TLA group and 22.9% with timolol (p=0.001).</p> <p>-17 patients withdrew due to adverse effects, 10 with TLA and 7 with timolol.</p>	-Timolol and timolol-LA were found to be statistically equivalent in ocular hypotensive efficacy.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
<p>Sherwood et al¹⁹ 2006</p>	<p>2 identical randomized, double-blinded, multicenter trials</p> <p>brimonidine/timolol fixed combination (BTFC) vs. brimonidine 0.2% vs. timolol 0.5%</p>	<p>N=1,159</p> <p>1 year</p>	<p>Patients diagnosed with ocular hypertension or glaucoma</p>	<p>-To compare efficacy (intraocular pressure (IOP) lowering effects from baseline with the listed treatments) and safety</p>	<p>-The mean decrease from baseline IOP in 12-month follow-up was 4.4 to 7.6 mm Hg BTFC, 2.7 to 5.5 mm Hg with brimonidine, and 3.9 to 6.2 mm Hg with timolol.</p> <p>-It was found that BTFC had significantly greater mean IOP reductions compared with timolol at all measurements ($p \leq 0.002$) and compared with brimonidine at 8 A.M., 10 A.M., and 3 P.M. measurements ($p < 0.001$) but not at 5 P.M.</p> <p>-Less adverse events were reported with the BTFC group than in the brimonidine group ($p = 0.006$).</p> <p>-More adverse events were reported with the BTFC group compared with the timolol group ($p < 0.001$).</p> <p>-Discontinuation rates due to adverse events were 14.3% with BTFC, 30.6% with brimonidine, and 5.1% with timolol.</p>	<p>-BTFC was found to be significantly more effective in lowering IOP as compared with either timolol or brimonidine individually.</p> <p>-Although BTFC was better tolerated than brimonidine, it was not as well tolerated as timolol.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Konstas et al ²⁴ 2005	Double-blind, two-center, crossover comparison latanoprost 0.005% vs. bimatoprost 0.03%	N=44 7 weeks	Diagnosis of primary open-angle glaucoma	To compare 24-hour diurnal intraocular pressure (IOP) -Patients had a glaucoma medicine washout period at start of study but did not when crossed over to other medication	-IOP readings were measured at six time points, at baseline, and after the first and second seven-week treatment periods. -At the end of the treatment periods, mean 24-hour IOP measurements were 17.3 ±2.8 mmHg for latanoprost and 16.7±2.4 mmHg for bimatoprost (p=0.01). -The largest difference in IOP was at 6 PM, favoring bimatoprost (p=0.008). -Conjunctival hyperemia was more common with bimatoprost (n=15) compared with latanoprost (n=6; p=0.004). -Two patients did not complete the study due to conjunctival hyperemia and ocular intolerance, both associated with bimatoprost therapy.	-In patients with primary open-angle glaucoma, the 24 hour diurnal IOP was statistically lower with bimatoprost as compared with latanoprost. -Due to the IOP measurements being small between the treatment groups, it may not be clinically meaningful. -Bimatoprost was associated with more conjunctival hyperemia compared with latanoprost.
Dirks et al ²⁵ 2006	Multicenter, randomized, double-blind clinical trial bimatoprost 0.03%	N=60 3 months	Diagnosed with normal-tension glaucoma	-To compare efficacy, including mean intraocular pressure (IOP) changes from baseline and safety of the treatments.	-Both active therapies had significant reductions in IOP compared to baseline at all diurnal measurements (p<0.001).	Both medications were efficacious; however, bimatoprost was more effective in lowering IOP levels.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	vs. latanoprost 0.005%			-Patients went through a washout period of all ocular hypotensive medications.	<p>-The morning (8 AM) measurement was significantly lower with bimatoprost at both follow-up visits ($p \leq 0.033$).</p> <p>-After three months, the mean IOP reductions from baseline were 2.8 to 3.8 mmHg (17.5-21.6%) with bimatoprost compared to 2.1 to 2.6 mmHg (12.7-16.2%) for latanoprost.</p> <p>-The overall mean reduction in IOP was greater with bimatoprost (3.4 mmHg, 19.9%) compared with latanoprost (2.3 mmHg, 14.6%; $p = 0.035$).</p> <p>-Adverse effects and clinical success did not differ between the two groups.</p>	
Coleman et al ³⁵ 2003	<p>Prospective, multicenter, randomized, double-blind clinical trial</p> <p>bimatoprost 0.03% vs. dorzolamide 2% and timolol 0.5%</p>	<p>N=177</p> <p>3 months</p>	<p>Patients diagnosed with glaucoma or ocular hypertension with inadequate control of intraocular pressure (IOP) after 2 weeks of timolol 0.5%</p>	<p>To compare IOP lowering effect, measured at baseline, week 1, and months 1, 2, and 3.</p>	<p>-Significantly greater IOP-lowering effects and better diurnal control occurred with bimatoprost as compared with DTFC.</p> <p>-Bimatoprost lowered mean IOP 6.8-7.6 mmHg from baseline at the 8AM measurements compared with the DTFC group that lowered IOP 4.4-5 mmHg from baseline ($p < 0.001$).</p>	<p>-It has been shown that bimatoprost consistently lowered IOP compared to DTFC in those patients with glaucoma or ocular hypertension not controlled on a beta-blocker alone.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	fixed combination (DTFC)		monotherapy.		<p>-A higher percentage achieved an IOP measurement less than 16 mmHg with bimatoprost at the 8AM 3-month visit compared with DTFC (p<0.008).</p> <p>-In the DTFC group, taste perversion, ocular burning, and stinging with instillation occurred more frequently than with bimatoprost.</p> <p>-Conjunctival hyperemia was more commonly reported with bimatoprost than with DTFC.</p>	
Simmons et al ³⁶ 2002	<p>Prospective, multicenter, double-blind, parallel-design clinical trial</p> <p>brimonidine 0.2% vs latanoprost 0.005%</p>	<p>N=115</p> <p>3 months</p>	<p>Patients diagnosed with uncontrolled glaucoma or ocular hypertension while currently on beta-blockers.</p>	<p>-To compare reduction in intraocular pressure (IOP) from baseline at peak drug effect, response, and quality of life.</p> <p>-Mean baseline IOP was comparable between treatment groups.</p>	<p>-After one month of therapy, if at least 15%reduction in IOP at peak effect was not achieved, patients were crossed over to the alternative study medication.</p> <p>-Response rates (at least 15% reduction in IOP at peak drug effect; p=0.963) and IOP reductions (p=0.798) were similar between brimonidine and latanoprost at one month.</p> <p>-Of the patients with successful IOP reduction at one month, the three-month mean IOP reductions were similar as well (4.55 mmHg</p>	<p>-Brimonidine and latanoprost provide comparable IOP lowering responses at peak drug effect as adjunctive therapy with beta-blockers.</p> <p>-Compared with latanoprost, brimonidine had a higher rate for being tolerated, with a smaller quantity of adverse events reported.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>reduction for brimonidine and 5.49 mmHg reduction for latanoprost; p=0.149).</p> <p>-At month 3, brimonidine and latanoprost kept at least a 15% additional reduction of IOP (p=0.314).</p> <p>-More negative quality-of-life variables were reported in the latanoprost group compared with the brimonidine group.</p> <p>-Significantly more patients on latanoprost complained of watery or teary eyes (p=0.025) and cold extremities (p=0.012) compared with brimonidine.</p>	
<p>DuBiner et al³⁷ 2001</p>	<p>Multicenter, double-blinded, parallel group, 4-visit study</p> <p>latanoprost Vs brimonidine</p>	<p>N=127</p> <p>3 months</p>	<p>Subjects diagnosed with ocular hypertension or glaucoma, and after washout had intraocular pressure (IOP) between 22 and 34.</p>	<p>% of patients with ≥20% reduction in IOP from baseline, as well as clinical success</p>	<p>-80% of those in the brimonidine group as compared with 74% in the latanoprost group had a ≥20% reduction in IOP.</p> <p>-Mean reduction in IOP was 6.7mmHg with brimonidine compared with 6.5mmHg with latanoprost.</p> <p>-A significantly higher percentage in the brimonidine group obtained an IOP reduction of ≥20% compared</p>	<p>-After 3 months, a significantly higher rate of non-response was seen with those treated with latanoprost compared with those treated with brimonidine.</p> <p>-A statistically significantly higher percentage treated obtained clinical success with brimonidine compared with latanoprost.</p> <p>-In those previously treated</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>with the latanoprost of those that were treatment-naïve(p=0.01)</p> <p>-In those patients that were previously treated, a greater % in the latanoprost group had a ≥20% reduction in IOP compared with the brimonidine group. This, however, was not statistically significant.</p> <p>-At the end of three months, significantly more brimonidine-treated patients obtained clinical success compared with those treated with latanoprost (p=0.01).</p>	<p>patients, however, latanoprost did provide a greater IOP reducing effect as compared with brimonidine.</p>
<p>Fechtner et al³⁸ 2004</p>	<p>Two parallel group, randomized, observer and patient blinded, multicenter, clinical trials</p> <p>Dorzolamide 2% /timolol 0.5% fixed combination (DTFC) vs. latanoprost 0.005%</p>	<p>Study 1: N=256 (conducted in the US)</p> <p>Study 2: N=288 (conducted in Europe/ Israel)</p> <p>3 months</p>	<p>Patients diagnosed with ocular hypertension or open-angle glaucoma.</p> <p>-Patients had a washout period if on prior ocular hypotensive medications to a baseline IOP of ≥24mmHg.</p>	<p>-To compare efficacy (daytime diurnal intraocular pressure (IOP)reduction from baseline) and tolerability</p> <p>-Measurements of IOP occurred at 8 A.M., 10 A.M., 2 P.M., and 4 P.M.</p>	<p>Study 1:</p> <p>-The mean daytime diurnal IOP was 18.9 mmHg for the DTFC group compared with 18.4mmHg for the latanoprost group after 3 months.</p> <p>Study 2</p> <p>-The mean daytime diurnal IOP was 17.4 mmHg for the DTFC group compared with 17.5 mmHg for latanoprost group.</p> <p>-Both therapies were well tolerated with only ocular stinging reported more frequently with DTFC compared with latanoprost.</p>	<p>-DTFC was seen to be equally effective in lowering IOP with latanoprost.</p> <p>-Even though ocular stinging was commonly reported with the DTFC group compared with latanoprost, both treatments were well tolerated.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Hollo et al ⁴⁰ 2006	Prospective, double-blind, randomized, active-controlled parallel study timolol 0.5% & travoprost 0.004% vs brinzolamide 1% & travoprost 0.004%	N=192 12 weeks	Patients diagnosed with ocular hypertension or primary open-angle glaucoma currently taking travoprost 0.004%	-To compare safety intraocular pressure (IOP) lowering effect from baseline of the treatments used as adjunctive therapy. -IOP measurements were recorded at the end of travoprost monotherapy and then 12 weeks after combination therapy.	-There were no significant differences between the two treatment groups for IOP reductions from baseline (levels measured at 18.1 mmHg on week 12 for both groups; p=0.96), each time point of IOP measurement throughout the day, or for the mean diurnal IOP (p>0.05). -In addition, significant differences were not observed for reported adverse effects. The most common adverse effect reported was conjunctival hyperemia, and it was reported more with brinzolamide (16%) compared with timolol (6%) treated patients (p=0.06).	-Timolol and brinzolamide were found to be equally efficacious when used as adjunctive treatment with travoprost for those with ocular hypertension of open-angle glaucoma. -Both treatments had a similar safety profile, with conjunctival hyperemia being reported more commonly with brinzolamide as compared to timolol.
Suzuki et al ⁴¹ 2006	Randomized, single-blind, parallel controls study travoprost 0.004% vs. dorzolamide 2% & timolol 0.5% fixed combination (DTFC)	N=56 6 week	-Patients diagnosed with Ocular hypertension or open-angle glaucoma -Baseline IOP readings and other patient demographics were similar between the groups.	To compare intraocular pressure (IOP) lowering effect from baseline of the two treatments -IOP measurements were taken at baseline, on week 3 and after 6 weeks of treatment	-The mean IOP reductions from baseline were 7.1 mmHg (30.7%) for travoprost and 4.5 mmHg (21.7%) for DTFC after six weeks of therapy. -Travoprost was observed to have significantly lower IOP readings at all time points (8 AM, 12 PM, 4 PM, and 8 PM) compared to DTFC (p<0.01).	-Travoprost was seen to provide significantly greater IOP lowering effects compared to DTFC in those with ocular hypertension or open-angle glaucoma.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					-Both medications were well tolerated, but taste perversion was more common in the DTFC group compared to the travoprost group.	
Orzalesi, et al ⁴⁸ 2006	Randomized, double-blind crossover study latanoprost 0.005% vs. travoprost 0.004% vs. bimatoprost 0.03%	N=44 1 month	Patients diagnosed with open-angle glaucoma or ocular hypertension	-To compare intraocular pressure (IOP) lowering effects between with the three medications -Treatment washout period occurred prior to randomization and baseline IOP levels were measured.	-Although all three medications were very effective for lowering IOP levels, they all had similar IOP reductions with no statistical differences. -All medications tested had significantly greater effects during the daytime than at night. -16% of the patients in this study experienced significantly higher nocturnal IOP than diurnal IOP.	-Latanoprost, travoprost, and bimatoprost were all clinically effective medications for reducing IOP levels in those patients with open-angle glaucoma or ocular hypertension.
Sharpe et al ⁴⁹ 2008	Prospective, double-masked, randomized, controlled, cross-over evaluation dorzolamide/timolol fixed combination (DTFC) vs bimatoprost	N=29 16 weeks	Open-angle glaucoma and intraocular pressure (IOP) \geq 21mmHg. Went through 6 week wash-out period and IOP between 22-29mmHg	Evaluation and comparison of efficacy and tolerability of two treatments if poorly controlled on latanoprost	-Crossover period included 2-8 week periods. Patients were randomized to one agent for 8 weeks during period 1 and then switched to the other agent during period 2. -The IOP range (p=0.02), IOP peak (p=0.003), and the treatment mean IOP (p=0.03) was significantly statistically lower with bimatoprost compared with DTFC. - DTFC and bimatoprost were comparable and no significant differences were found at individual	-Patients diagnosed with open-angle glaucoma can acquire comparable control with DTFC and bimatoprost when you compare IOP measurements at individual time points. -Bimatoprost has statistically improved diurnal control when compared with DTFC.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>time points.</p> <p>-Bimatoprost was better tolerated than DTFC, with stinging or burning occurring more frequently with DTFC than bimatoprost ($p \leq 0.0001$).</p>	
Vold et al ⁴⁶ 2008	<p>Prospective, double-masked, parallel-group, randomized, clinical trial</p> <p>brinzolamide/ timolol fixed combination (BTFC) Vs dorzolamide/ Timolol fixed combination (DTFC)</p>	<p>N=47</p> <p>1 week</p>	<p>Diagnosis of open-angle glaucoma or ocular hypertension</p>	<p>Evaluation of ocular discomfort of two treatments.</p> <p>-Ocular discomfort assessments were filled out by patients at baseline on their current intraocular pressure (IOP) treatment as well as at the end of 1 week while on study medication.</p>	<p>-Those in the BTFC treatment group resulted in significantly lower mean ocular discomfort scores compared with those treated with DTFC ($p=0.0003$).</p> <p>-Statistically significant increases were seen from baseline in the ocular discomfort scores with both treatment groups, but the BTFC group had a smaller increase ($p=0.0028$) compared with the DTFC group ($p<0.0001$).</p> <p>-49% of the BTFC group compared with 15% of the DTFC group reported no ocular discomfort after 1 week of treatment ($p=0.0004$).</p>	<p>-BTFC was associated with statistically significant less ocular discomfort than DTFC.</p>
Day et al ²⁸ 2008	<p>Randomized, single-center, investigator-masked, parallel-group clinical study</p>	<p>N=40</p>	<p>Patients with intraocular pressure (IOP) ≥ 18mmHg receiving latanoprost</p>	<p>-Evaluate efficacy and tolerability of two treatments.</p> <p>-Baseline IOP was measured 3 times (8AM, 10AM, and 4PM) while patients</p>	<p>-Mean diurnal IOP at baseline was similar between the two treatment groups.</p> <p>-Mean diurnal IOP at end of 3 months was significantly lower with the brimonidine treatment group (16.3 ± 2.63mmHg) compared with</p>	<p>-Significantly lower IOP levels were observed in those in the brimonidine treatment group as compared with the brinzolamide treatment group when used as adjunctive therapy with latanoprost to treat glaucoma or ocular hypertension.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	brimonidine 0.1% & latanoprost 0.005% vs brinzolamide 1% & latanoprost 0.005%	3 months		only on latanoprost, then was measured at 1 and 3 months after initiated adjunctive therapy	<p>the brinzolamide treatment group (17.8+/-2.19mmHg) (p=0.028).</p> <p>-Both at 10pm (p<0.001) and 4pm (p=0.050) IOP measurements brimonidine supplied a greater lowering of IOP when compared to brinzolamide. IOP lowering was equivalent between the two groups at the 8am measurement (p=0.716).</p> <p>-Adverse events more commonly seen with brinzolamide use included blurred vision at month 1 and bitter taste at months 1 and 3.</p>	<p>-Although both treatments were well tolerated, adverse events were more common with brinzolamide.</p> <p>-Limitations of this study include single site and small sample size, so additional studies are warranted.</p>
Kaback et al ²⁷ 2008	<p>Randomized, double-masked, parallel group, multicenter study</p> <p>brinzolamide 1%/timolol 0.5% fixed combination (BTFC) Vs brinzolamide 1% or timolol 0.5%</p>	<p>N=523</p> <p>6 months</p>	<p>Patients diagnosed with open-angle glaucoma or have ocular hypertension.</p> <p>After a washout period, IOP levels must have been within 24-36mmHg range at 8am and 21-36mmHg range at 10am on different visits</p>	<p>Compare efficacy (intraocular pressure(IOP) lowering effect) and safety of the two treatments</p>	<p>-IOP lowering effects from baseline of the BTFC group (8-8.7mmHg range) was found to be both clinically and statistically significant compared to the brinzolamide (5.1-5.6mmHg) or the timolol group (5.7-6.9mmHg).</p> <p>-Safety issues were not present when reviewed adverse events reported.</p>	<p>-BTFC IOP lowering effect is superior compared to brinzolamide or timolol monotherapy.</p>

CONTRAINDICATIONS ⁵⁴⁻⁷²

All medications in this therapeutic class carry a contraindication of hypersensitivity to their active ingredient or to any component of the compound. There are several drugs in particular that carry their own contraindications unique to the class. These contraindications are listed in the table below. Please note that Cosopt®, a combination of dorzolamide and timolol have the same contraindications as listed in the individual ingredients.

Drug	Contraindication
betaxolol (Betoptic S®)	Cardiogenic shock, overt cardiac failure, second and third degree AV block, severe sinus bradycardia
brimonidine (Alphagan P®) (Alphagan®)	Patients taking MAO-I therapy
brimonidine/timolol (Combigan®)	Bronchial asthma or a history of asthma, severe COPD, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock
carbachol (Isopto Carbachol®) (Carboptic®)	Acute iritis
carteolol	Severe COPD, asthma, sinus bradycardia, second & third degree AV block, severe heart failure, cardiogenic shock
dipivefrin (Propine®)	Narrow-angle glaucoma
echothiophate iodide (Phospholine Iodide®)	Active uveal inflammation and angle closure glaucoma
latanoprost (Xalatan®)	Hypersensitivity to benzalkonium chloride
levobunolol (Betagan®)	Sinus bradycardia, asthma, COPD history, second or third degree AV blocks, cardiac insufficiency
metipranolol (Optipranolol®)	Bronchial asthma, or a history of bronchial asthma, severe COPD, symptomatic bradycardia, second or third degree AV block, cardiogenic shock, cardiac failure.
pilocarpine (Isopto Carpine®) (Pilopine HS®)	Acute iritis or glaucoma after cataract extraction

Drug	Contraindication
timolol (Timoptic®) (Istalol®) (Betimol®)	Asthma, COPD, severe heart failure, second or third degree AV block, sinus bradycardia, cardiogenic shock

SPECIAL POPULATIONS ⁵⁴⁻⁷²

There was no information provided for requiring dosage change in those with hepatic insufficiency. There was only one medication listed that indicated use should be avoided with renal insufficiency.

Drug	Pediatrics	Pregnancy Category	Dosage change for Renal Insufficiency
betaxolol (Betoptic S®)	0.5% soln: No	C	
bimatoprost (Lumigan®)	No	C	
brimonidine (Alphagan P®) (Alphagan®)	0.2% soln: No 0.1% & 0.15% soln: >2 yrs (dosed same as adult)	B	
brimonidine/timolol (Combigan®)	≥2 yrs	C	
brinzolamide (Azopt®)	No	C	
carbachol (Isopto Carbachol®) (Carboptic®)	No	C	
carteolol	No	C	
dipivefrin (Propine®)	No	B	
dorzolamide (Trusopt®)	> 2 yrs	C	Avoid use with CrCl < 30

Drug	Pediatrics	Pregnancy Category	Dosage change for Renal Insufficiency
dorzolamide/ timolol (Cosopt®)	> 2 years old	C	
echothiophate iodide (Phospholine Iodide®)	No	C	
latanoprost (Xalatan®)	No	C	
levobunolol (Betagan®)	No	C	
metipranolol (Optipranolol®)	No	C	
pilocarpine (Isopto Carpine®) (Pilopine HS®)	No	C	
timolol (Timoptic®) (Istalol®) (Betimol®)	No	C	
travoprost (Travatan®) (Travatan Z®)	No	C	

ADVERSE DRUG REACTIONS ⁵⁴⁻⁷²

Brinzolamide may cause less burning and stinging than dorzolamide. Travoprost has 30-50% incidence of ocular hyperemia occurring. The most common adverse reactions include blurred vision, headache, ocular burning, and photophobia. Carbachol and pilocarpine, not listed in the table below, carry an adverse reaction of blurred vision. Carbachol also can cause ocular burning/pain. Levobunolol, another medication not listed, also carries an adverse reaction of headache and ocular burning.

Brimonidine/timolol side effects listed in the table below were those reported during 12 month trials with the drug. These do not include other adverse reactions reported with individual components.

All numbers listed in the table below are expressed as percentages. Other than those mentioned, the specific incidence of adverse reactions were not available.

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Drug	BETA	BIM	BRIM	BRIM /TIM	BRIN	CART	DIP	DOR	DOR /TIM	ECH	LAT	MET	TIM	TRAV
Abnormal vision	-	-	-	-	-	-	-	-	-	-	-	√	-	1-4
Allergic conjunctivitis	-	1-3	-	√	-	-	-	-	-	-	-	-	-	-
Bitter/unusual taste	-	-	-	-	5-10	-	-	√	≤30	-	-	-	-	-
Blepharitis	-	3-10	-	√	1-5	-	-	-	1-5	√	-	√	-	1-4
Blurred Vision	√	15-45	-	-	5-10	-	√	√	5-15	√	√	√	-	-
Brow ache	-	-	-	-	-	-	-	-	-	√	-	√	-	-
Cataract	-	3-10	-	-	-	-	-	-	1-5 ¹	-	-	-	-	1-4
Conjunctival edema	-	1-3	-	√	-	-	-	-	1-5	-	-	-	-	-
Conjunctival hyperemia	-	15-45	√	√	-	-	-	-	5-15	-	-	-	√	-
Conjunctivus	-	-	√	-	-	-	-	-	1-5	-	-	√	-	1-4
Dizziness	-	-	-	-	-	√	-	-	1-5	-	-	√	√	-
Dry Eye	√	3-10	-	√	1-5	-	-	-	1-5	-	√	-	√	1-4
Dry Mouth	-	-	√	-	-	-	-	-	-	-	-	-	√	-
Eye Discomfort	√	3-10	-	-	-	-	-	-	1-5	-	-	-	-	5-10
Foreign Body Sensation	√	3-10	-	√	1-5	-	-	-	1-5	-	√	-	√	5-10
Headache	-	1-5	-	√	1-5	√	√	√	1-5	-	-	√	√	1-5
↑ in iris pigmentation	-	1-3	-	-	-	-	-	-	-	-	√	-	-	1-4

Drug	BETA	BIM	BRIM	BRIM /TIM	BRIN	CART	DIP	DOR	DOR /TIM	ECH	LAT	MET	TIM	TRAV
Itchy Eyes	√	-	-	-	-	-	-	-	5-15	-	√	-	-	-
Keratitis	√	-	-	-	1-5	-	-	√	5-15	-	√	-	-	1-4
Myopia	-	-	-	-	-	-	-	-	-	√	-	-	-	-
Ocular allergic reactions	√	-	-	-	-	-	√	√	-	-	-	√	-	1-5
Ocular Burning	-	3-10	√	√	-	√	√	√	≤30	√	√	-	√	-
Ocular inflammation	√	3-10	-	-	1-5	√	√	-	-	√	-	-	√	-
Ocular Pain	√	-	-	-	1-5	-	√	-	1-5	√	√	-	√	5-10
Ocular Pruritus	-	15-45	√	√	1-5	-	-	-	-	-	-	-	√	5-10
Photophobia	√	1-3	-	-	-	√	√	√	-	-	√	√	√	1-4

BETA-betaxolol (Betoptic® S); BIM-bimatoprost (Lumigan®); BRIM-brimonidine (Alphagan®/P); BRIM/TIM-brimonidine/timolol (Combigan®); BRIN-brinzolamide (Azopt®); CART- carteolol; DIP-dipivefrin (Propine®); DOR-dorzolamide (Trusopt®); DOR/TIM (dorzolamide/timolol-Cosopt®); ECH-echothiophate (Phospholine); LAT- latanoprost (Xalatan®); MET- metipranolol (Optipranolol); TIM-timolol (Timoptic®/XE, Istalol®, Betimol®); TRAV- travoprost (Travatan®/Z)

¹ post-subcapsular

DRUG-DRUG INTERACTIONS ⁵⁴⁻⁷²

Unless listed in the tables below, there were not any significant clinical drug interactions found or known.

betaxolol (Betoptic S®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Clonidine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Reserpine		

brimonidine (Alphagan P®, Alphagan®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Antihypertensives	Possible additive reduction of pulse/BP	Possible hypotension/bradycardia; monitor combination.
Beta-blockers		
CNS depressants	Possible additive CNS depression	Monitor combination.
Digoxin	Possible additive reduction of pulse/BP	Possible hypotension/bradycardia; monitor combination.
MAO inhibitors	Additive MAO inhibition	Avoid concomitant use.

brimonidine/timolol (Combigan®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Antihypertensives	Possible additive reduction of pulse/BP	Possible hypotension/bradycardia; monitor combination.
Beta-blockers	Possible additive beta-blockade	Concomitant use not recommended.
Calcium-channel blockers	Possible AV conduction disturbances	Possible left ventricular failure/hypotension; avoid concomitant use in patients with impaired cardiac function.
Clonidine	Possible additive catecholamine depletion	Possible hypotension/bradycardia; monitor combination.
Digoxin	Possible additive reduction of pulse/BP	
MAO inhibitors	Possible ↓ brimonidine metabolism	Possible hypotension; use with caution.
Reserpine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
SSRIs	Inhibition of timolol metabolism by CYP2D6	Possible ↓ heart rate; possible ↑ depression; monitor combination.

brinzolamide (Azopt®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Oral carbonic anhydrase inhibitors (e.g. acetazolamide, methazolamide)	Additive effects	Avoid concomitant use.

carteolol (Ocupress®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Clonidine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.
Reserpine		

dorzolamide (Trusopt®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Oral carbonic anhydrase inhibitors	Additive effects	Avoid concomitant use.

dorzolamide/timolol (Cosopt®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Calcium-channel blockers	Possible AV conduction disturbances	Possible left ventricular failure/hypotension; avoid concomitant use in patients with impaired cardiac function.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Clonidine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.
Oral carbonic anhydrase inhibitors	Additive effects	Avoid concomitant use.
Quinidine	Potentiated systemic beta-blockade due to inhibition of timolol metabolism by CYP2D6	Possible hypotension or bradycardia; monitor combination.
Reserpine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.

echothiophate iodide (Phospholine Iodide®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Cholinesterase inhibitors	Potential of cholinesterase inhibition	Avoid concomitant use.

levobunolol (Betagan®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Calcium-channel blockers	Possible AV conduction disturbances	Possible left ventricular failure/hypotension; avoid concomitant use in patients with impaired cardiac function.

metipranolol (Optipranolol®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Calcium-channel blockers	Possible AV conduction disturbances	Possible left ventricular failure/hypotension; avoid concomitant use in patients with impaired cardiac function.
Clonidine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.
Reserpine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.

timolol (Timoptic®/ Istalol®)

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Possible additive beta-blockade	Monitor combination.
Calcium-channel blockers	Possible AV conduction disturbances	Possible left ventricular failure/hypotension; avoid concomitant use in patients with impaired cardiac function.
Clonidine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.
Reserpine	Possible additive catecholamine depletion	Possible hypotension or bradycardia; monitor combination.
Quinidine	Potentiated systemic beta-blockade due to inhibition of timolol metabolism by CYP2D6	Possible hypotension or bradycardia; monitor combination.

SUMMARY

The availability to have a wide variety of agents for the treatment of glaucoma is important, as patients often require a combination of therapies to achieve adequate control of elevated IOP. Currently, no available guideline suggests any one class should be used as first line therapy; however, safety and tolerability of the medications should play a role in product selection.^{1,53} The target IOP reductions are typically 20 to 30 percent²³, and even up to 50 percent below baseline. Beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs are the mainstays of therapy. The β_1 selectivity of betaxolol (Betoptic®, Betoptic® S) may be an advantage in patients with cardiac or pulmonary co-morbidities. Direct-acting miotics, including pilocarpine are second or third line therapy now due to frequent administration and lower tolerability. Although not routinely used today, these agents serve unique niches in therapy. Adequate treatment of glaucoma requires a high level of adherence to therapy for treatment success.¹

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

Although there are a significant number of head-to-head trials, many were small, had flaws, or produced contradictory results. Thus, there is insufficient evidence to suggest that the glaucoma medications differ within subclasses (based on mechanism of action) in regards to efficacy, safety, tolerability, or clinical outcomes in the treatment of glaucoma.

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