



Oregon State Drug Use Research & Management Program
UNIVERSITY

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079

College of Pharmacy Phone 503-945-5220 | Fax 503-947-1119



Abbreviated Update: Ophthalmic Glaucoma Agents

Month/Year of Review: November 2014

PDL Class: Ophthalmic Glaucoma

Literature Search End Date: July 2014

Date of Last Review: August 2012

Source Document: OSU College of Pharmacy

Current Preferred Agents: BETAXOLOL, BRIMONIDINE (ALPHAGAN AND ALPHAGAN P), BRINZOLAMIDE (AZOPT), CARTEOLOL, DORZOLAMIDE/TIMOLOL, LATANOPROST, PILOCARPINE GEL AND DROPS, and TRAVOPROST (TRAVATAN Z[®]).

Current Non-preferred Agents: ACETAZOLAMIDE, ACETYLCHOLINE CHLORIDE (MIOCHOL-E), ALPHAGAN[®] P, ALPRACLONIDINE (IOPIDINE), AZOPT[®], BETAXOLOL (BETOPIC[®] S), COMBIGAN[®], CARBACHOL (CARBASTAT), DORZOLAMIDE, DEMECARIUM (HUMORSOL), BIMATOPROST (LUMIGAN[®]), LEVOBUNOLOL, METHAZOLAMIDE, BRINZOLAMIDE/BRIMONIDINE (SIMBRINZA[®]), ZIOPTAN[®], AND RESCULA[®], TIMOLOL, METIPRANOLOL,

Previous Recommendations:

- Continuing to include a medication from each category including miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, and prostaglandin analogues as preferred on the preferred drug list (PDL).
- Make generic lantanoprost and travapost as preferred on the PDL; Zioptin, Alphagan P, and aprochonidine remain as non-preferred.

PA Criteria/QL: None.

Recommendations:

- Keep Simbrinza as non-preferred on PDL due to lack of evidence that there is a difference in efficacy or safety compared to other combination products.
- No further research or review needed at this time and evaluate comparative costs in executive session.

Methods:

A MEDLINE OVID search was conducted using all ophthalmic glaucoma agents limited to randomized controlled trials, systematic review, meta-analysis, English language, and conducted in humans since the literature search conducted for the previous review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New drugs/formulations:

In April 2013 FDA approved a combination product Simbrinza[®] (brinzolamide 1%/brimonidine 0.2%) suspension to lower the intraocular pressure in patients with open angle glaucoma or ocular hypertension¹. The approval was based on two published randomized trials^{2,3}. Both trials were factorial-design double-masked, Phase 3 safety and efficacy clinical trials compared brinzolamide 1%/brimonidine 0.2% (BBFC) to each of the two components as primary end point. Intra-ocular pressure (IOP) was measured at 4 time points during each of 4 visits (baseline, Week 2, Week 6, and Month 3). Study C-10-033³ enrolled 660 patients at 68 sites and Study C-10-039² enrolled 690 at 64 sites in the US. The results of study C-10-033 showed at 3 months, the mean IOP of the brinzolamide-brimonidine group (16.3-19.8 mm Hg) was significantly lower than that of either the brinzolamide group (19.3-20.9 mm Hg; $P \leq .002$) or the brimonidine group (17.9-22.5 mm Hg; $P < .001$) across all time points³. Study C-10-039 also concluded with similar results that mean IOP of the BBFC group was significantly lower than that of either the brinzolamide group or the brimonidine group ($P \leq 0.005$) across all time points. Common adverse reactions reported in these studies were essentially analogous to adverse reactions previously reported with one or the other ingredient when used in treatment of IOP. Most common adverse reactions occurring in approximately 3 to 5% of patients included blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, eye allergy.

New FDA Indications:

None identified.

New FDA safety alerts:

None identified.

New Systematic Reviews:

Quranta L et al.⁴ conducted a systematic review and meta-analysis on the intraocular pressure (IOP) – lowering effect of prostaglandin analogs (PGAs) administered in combination with Beta-blockers in patients with glaucoma or ocular hypertension. The efficacy endpoint was the mean difference (MeD) in the reduction in IOP from baseline; the tolerability was the incidence of hyperemia. The review included 18 trials using PGAs and timolol as monotherapy (Mt) or in fixed (FC) or unfixed combinations (UC) with total of 23 comparisons of FC vs. Mt, and 5 of FC vs. UC. The FCs were less efficacious than UCs (MeD: 0.69, 95% CI: 0.29 to 1.08). In comparison with timolol Mt, the latanoprost/timolol FC led to a greater IOP reduction (MeD: -2.74, 95% CI: -3.24 to -2.23) than the bimatoprost/timolol FC (MeD: -1.49, 95% CI: -1.86 to -1.12) or the travoprost/timolol FC (MeD: -1.93, 95% CI: -2.98 to -0.88). The FCs led to a lower hyperemia risk than UCs [relative risk (RR): 0.70, 95% CI: 0.43 to 1.14] and PGA Mt (RR: 0.61, 95% CI: 0.53 to 0.70). The authors concluded FCs are more efficacious than their individual components, but less efficacious than their respective UCs. FCs lead to a lower hyperemia risk than UCs and their respective PGA Mts.

Chang JW⁵ 2012 performed a systematic review and meta-analysis to evaluate IOP – lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol. Forty-one randomized clinical trials with primary open angle glaucoma (POAG) or ocular hypertension (OHT). The main efficacy measures were the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP reduction on the diurnal IOP curve. The relative reductions for mean diurnal IOP were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. For the highest IOP decrease, relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol; for the lowest IOP decrease, those varied from 25.9% for dorzolamide/timolol to 33.1% for bimatoprost/timolol. Both latanoprost/timolol and travoprost/timolol were more effective in lowering mean diurnal IOP than brimonidine/timolol (WMD: 5.9 and 7.0) and dorzolamide/timolol (WMD: 3.8 and

3.3). The conclusions from the review were that six commonly used fixed-combination drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travapost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.

Guidelines:

None identified.

New Trials:

A total of 105 citations resulted from initial literature search. After inclusion for further review, 24 were evaluated further and 3 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (**Appendix 1**). These trials are briefly described in Table 1:

Table 1: Potential Relevant New Trials

Study	Comparison	Population	Primary Outcome	Results
Shoji T, et al. ⁶ 2013	Travoprost plus timolol (TTFC) and latanoprost plus timolol fixed combinations (LTFC)	Normal-tension glaucoma	Reduction of ocular pressure from baseline.	The mean baseline IOP was 14.8 ± 3.3 mm Hg (95% confidence interval [CI], 14.1-15.3 mm Hg) for treatment with DTFC. Mean reduction in IOP at 12 weeks was significantly greater in the TTFC group than in the LTFC group (-2.4 ± 2.3 mm Hg vs. -1.1 ± 2.3 mm Hg; P = 0.021).
Delval L et al. ⁷ 2013	Unpreserved timolol 0.1% gel vs. preserved latanoprost 0.005%	Glaucoma	Reduction of the sum of the scores of the eight ocular symptoms, the six objective signs and IOP.	At D84, 91.5% of patients were responders to the primary combined efficacy/safety criteria under unpreserved timolol gel treatment versus 48.6% under latanoprost treatment (P<0.001). Both signs and symptoms were significantly improved (P<0.001) with unpreserved timolol gel compared to preserved latanoprost.
Day DG et al. ⁸ 2013	Bimatoprost 0.03% preservative-free (PF) ophthalmic solution vs. bimatoprost 0.03% (Lumigan)	Open-angle glaucoma or ocular hypertension	Non-inferiority was change from baseline in worse eye intraocular pressure (IOP) in the per-protocol population at week 12.	Both treatments showed decreases in mean average eye IOP at all follow-up time points (p<0.001)

RCT = Randomized control trial; DM = double masked; MC = multi-center; PC = placebo control; PG: Parallel group

References:

1. Simbrinza Prescribing Information. Available at: http://ecatalog.alcon.com/pi/simbrinza_us_en.pdf. Accessed August 9, 2014.
2. Whitson J, Realini, Nguyen, McMenemy, Goode. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clinical Ophthalmology*. 2013;1053. doi:10.2147/OPHTH.S46881.
3. Katz G, DuBiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724-730. doi:10.1001/jamaophthalmol.2013.188.
4. Quaranta L, Biagioli E, Riva I, et al. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther*. 2013;29(4):382-389. doi:10.1089/jop.2012.0186.
5. Cheng J-W, Cheng S-W, Gao L-D, Lu G-C, Wei R-L. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. *PLoS ONE*. 2012;7(9):e45079. doi:10.1371/journal.pone.0045079.
6. Shoji T, Sato H, Mizukawa A, et al. Hypotensive effect of latanoprost/timolol versus travoprost/timolol fixed combinations in NTG patients: a randomized, multicenter, crossover clinical trial. *Invest Ophthalmol Vis Sci*. 2013;54(9):6242-6247. doi:10.1167/iovs.13-11942.
7. Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B, Diamant Study Group. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. *J Fr Ophthalmol*. 2013;36(4):316-323. doi:10.1016/j.jfo.2012.04.015.
8. Day DG, Walters TR, Schwartz GF, et al. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. *Br J Ophthalmol*. 2013;97(8):989-993. doi:10.1136/bjophthalmol-2012-303040.

Appendix 1: Abstract of RCTs and Systematic Reviews

1. Whitson J, Realini, Nguyen, McMenemy, Goode. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clinical Ophthalmology*. 2013;1053.

Abstract

Background: The objective of this study was to examine the safety and intraocular pressure (IOP)-lowering efficacy of a fixed combination of brinzolamide 1% + brimonidine 0.2% (BBFC) after six months of treatment in patients with open-angle glaucoma or ocular hypertension.

Methods: This was a randomized, multicenter, double-masked, three-month, three-arm contribution-of-elements study with a three-month safety extension. Patients were randomly assigned 1:1:1 to treatment with BBFC, brinzolamide 1%, or brimonidine 0.2% after a washout period. Patients dosed their study medications three times daily at 8 am, 3 pm, and 10 pm for six months. Patients returned for visits at two weeks, six weeks, three months, and six months. IOP measurements were used to assess efficacy. Safety assessments were adverse events, corrected distance visual acuity, slit-lamp biomicroscopy, pachymetry, perimetry, fundus parameters, and cardiac parameters.

Results: A total of 690 patients were randomized. Six-month mean IOP values were similar to those at three months, when the mean IOP in patients treated with BBFC was significantly lower than that of either monotherapy group. A total of 175 patients experienced at least one treatment-related adverse event (BBFC, 33.0%; brinzolamide, 18.8%; brimonidine, 24.7%), eight of which were severe, and five resulted in discontinuation. Seventy-seven patients discontinued participation due to treatment-related adverse events (BBFC, 17.2%; brinzolamide, 2.1%; brimonidine, 14.5%). There were 21 serious adverse events (n = 7 in each group), none of which was related to treatment. Resting mean pulse and blood pressure with BBFC were similar to those with brimonidine, demonstrating modest, clinically insignificant decreases. No new or increased risks were identified with use of BBFC relative to either monotherapy.

Conclusions: This study showed that, after six months of treatment, the safety profile of BBFC was similar to that of its individual components and its IOP-lowering activity was similar to its efficacy at three months, when it was superior to both brinzolamide 1% alone and brimonidine 0.2% alone.

2. Katz G, DuBiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724-730.

Abstract

Importance: This study evaluates the contribution of the individual components of an investigational non- β -antagonist fixed combination of brinzolamide, 1%, and brimonidine, 0.2%. This study and its sister study provide the first randomized data showing the intraocular pressure (IOP)-lowering activity and the toxicity profile of this novel topical antihypertensive fixed combination.

Objective: To compare IOP-lowering efficacy of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%, with that of its components in patients with open-angle glaucoma or ocular hypertension.

Design: In this phase 3, double-masked, parallel-group, multicenter study, eligible patients were randomized 1:1:1 to treatment with fixed-combination brinzolamide, 1%, and brimonidine, 0.2%; brinzolamide, 1%; or brimonidine, 0.2%, 3 times daily for 3 months.

Setting: Sixty-six academic and private practice study sites throughout the United States.

Participants: A total of 660 adults with a clinical diagnosis of open-angle glaucoma or ocular hypertension from a referred sample were enrolled. Thirty-four patients discontinued participation due to treatment-related nonserious adverse events.

Intervention: Topical administration of study medication (fixed-combination brinzolamide, 1%, and brimonidine, 0.2%; brinzolamide, 1%; or brimonidine, 0.2%) 1 drop 3 times daily for 3 months.

Main outcomes and measures: Mean IOP at the 3-month visit at all time points (8 AM, 10 AM, 3 PM, and 5 PM).

Results: A total of 660 patients were enrolled. Baseline mean IOP values were similar among treatment groups at all 4 time points. At 3 months, the mean IOP of the brinzolamide-brimonidine group (16.3-19.8 mm Hg) was significantly lower than that of either the brinzolamide group (19.3-20.9 mm Hg; $P \leq .002$) or the brimonidine group (17.9-22.5 mm Hg; $P < .001$) across all time points. One of 10 serious adverse events (chest pain, brinzolamide group) was judged as treatment related. A total of 129 patients experienced at least 1 treatment-related adverse effect (brinzolamide-brimonidine, 22.9%; brinzolamide, 18.6%; and brimonidine, 17.3%; $P = .31$), most of which were ocular.

Conclusions and relevance: This registrational study provides evidence that the fixed combination of brinzolamide, 1%, and brimonidine, 0.2%, can safely and effectively lower IOP in patients with open-angle glaucoma or ocular hypertension, showing significantly superior IOP-lowering activity compared with either brinzolamide or brimonidine monotherapy while providing a safety profile consistent with that of its individual components.

3. **Shoji T, Sato H, Mizukawa A, et al. Hypotensive effect of latanoprost/timolol versus travoprost/timolol fixed combinations in NTG patients: a randomized, multicenter, crossover clinical trial. *Invest Ophthalmol Vis Sci.* 2013;54(9):6242-6247.**

Abstract

Purpose: To compare the ocular hypotensive effect of travoprost plus timolol (TTFC) and latanoprost plus timolol fixed combinations (LTFC) in patients with normal-tension glaucoma (NTG).

Methods: A two-sequence 12-week, multicenter, prospective, randomized, single-blinded, crossover clinical trial examined 59 NTG patients. If both eyes were eligible, only one eye (chosen at random) was used for analytical purposes. After a 12-week run-in period with dorzolamide plus timolol fixed combination (DTFC), patients were randomized into one of the two crossover sequences of treatment for 12 weeks with TTFC or LTFC and were subsequently crossed over to the alternative treatment for a further 12 weeks. The primary endpoint was reduction in IOP after 12 weeks of each treatment sequence. The effect of treatment on IOP was assessed using a linear mixed model.

Results: The mean baseline IOP was 14.8 ± 3.3 mm Hg (95% confidence interval [CI], 14.1-15.3 mm Hg) for treatment with DTFC. The TTFC treatment period showed consistently lower mean IOP compared with LTFC treatment period at all measurement time points. Mean reduction in IOP at 12 weeks was significantly greater in the TTFC group than in the LTFC group (-2.4 ± 2.3 mm Hg vs. -1.1 ± 2.3 mm Hg; $P = 0.021$). No interaction between the drug and treatment sequence was detected. The effects of intraocular lens implantation and measurement time were also not significant. The tolerability profiles of both treatments were similar.

Conclusions: The additional reduction in IOP was greater with TTFC than with LTFC, and their tolerability profiles were similar.

4. **Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B, Diamant Study Group. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. *J Fr Ophtalmol.* 2013;36(4):316-323.**

Abstract

Purpose: To assess the safety and efficacy of unpreserved timolol 0.1% gel in ocular hypertensive (OHT) or glaucomatous patients controlled by preserved latanoprost 0.005% but with signs of ocular intolerance.

Methods: Patients initially treated with preserved latanoprost were randomized to receive once daily either one drop of unpreserved timolol gel in the morning or one drop of preserved latanoprost in the evening for 84 days. All patients attended three visits (D0, D28 and D84). A patient was considered as responder to primary criteria at Day 84 if the sum of the scores of the eight ocular symptoms and the six objective signs had decreased by at least 20% and if the effect on intra-ocular pressure (IOP) was assessed as either satisfactory or acceptable.

Results: At D84, 91.5% of patients were responders to the primary combined efficacy/safety criteria under unpreserved timolol gel treatment versus 48.6% under latanoprost treatment ($P<0.001$). As early as D28, 85.3% of patients were responders in the unpreserved timolol gel group compared to 40.3% of patients in the preserved latanoprost group ($P<0.001$). IOP change from baseline was not significant between treatments ($P>0.05$) at D28 or D84. Both signs and symptoms were significantly improved ($P<0.001$) with unpreserved timolol gel compared to preserved latanoprost.

Conclusions: Unpreserved timolol 0.1% gel maintained the efficacy of preserved latanoprost and reduced signs and symptoms of intolerance in almost all glaucomatous/OHT patients on preserved latanoprost.

5. **Day DG, Walters TR, Schwartz GF, et al. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. *Br J Ophthalmol.* 2013;97(8):989-993.**

Abstract

Background/Aim: To evaluate efficacy and safety of bimatoprost 0.03% preservative-free (PF) ophthalmic solution versus bimatoprost 0.03% (Lumigan) ophthalmic solution for glaucoma or ocular hypertension.

Methods: In this double-masked, parallel-group study, patients were randomised to bimatoprost PF or bimatoprost for 12 weeks. The primary analysis for non-inferiority was change from baseline in worse eye intraocular pressure (IOP) in the per-protocol population at week 12. For equivalence, it was average eye IOP in the intent-to-treat population at each time point at weeks 2, 6 and 12.

Results: 597 patients were randomised (bimatoprost PF, $n=302$ and bimatoprost, $n=295$). The 95% CI upper limit for worse eye IOP change from baseline was <1.5 mm Hg at each week 12 time point, meeting prespecified non-inferiority criteria. The 95% CI upper limit for the treatment difference for average IOP was 0.69 mm Hg and the lower limit was -0.50 mm Hg at all follow-up time points (hours 0, 2 and 8 at weeks 2, 6 and 12), meeting equivalence criteria. Both treatments showed decreases in mean average eye IOP at all follow-up time points ($p<0.001$), were safe and well tolerated.

Conclusions: Bimatoprost PF is non-inferior and equivalent to bimatoprost in its ability to reduce IOP-lowering with a safety profile similar to bimatoprost.

6. Quaranta L, Biagioli E, Riva I, et al. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2013;29(4):382-389.

Abstract

Purpose: To estimate the intraocular pressure (IOP)-lowering effect of prostaglandin analogs (PGAs) administered in combination with β -blockers.

Methods: We searched the Medline and Embase databases for randomized trials comparing topical therapies with PGAs and timolol administered as monotherapy (Mt), or in fixed (FC) or unfixed combinations (UC) to patients with glaucoma or ocular hypertension. The efficacy endpoint was the mean difference (MeD) in the reduction in IOP from baseline; the tolerability endpoint was the incidence of hyperemia.

Results: The 18 eligible trials involved 23 comparisons of FC versus Mt, and 5 of FC versus UC. The FCs were less efficacious than UCs (MeD: 0.69, 95% CI: 0.29 to 1.08). In comparison with timolol Mt, the latanoprost/timolol FC led to a greater IOP reduction (MeD: -2.74, 95% CI: -3.24 to -2.23) than the bimatoprost/timolol FC (MeD: -1.49, 95% CI: -1.86 to -1.12) or the travoprost/timolol FC (MeD: -1.93, 95%CI: -2.98 to -0.88). The FCs led to a lower hyperemia risk than UCs [relative risk (RR): 0.70, 95% CI: 0.43 to 1.14] and PGA Mt (RR: 0.61, 95% CI: 0.53 to 0.70).

Conclusions: FCs are more efficacious than their individual components, but less efficacious than their respective UCs. FCs lead to a lower hyperemia risk than UCs and their respective PGA Mts.

7. Cheng J-W, Cheng S-W, Gao L-D, Lu G-C, Wei R-L. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. *PLoS ONE.* 2012;7(9):e45079.

Abstract

Background: The first goal of medical therapy in glaucoma is to reduce intraocular pressure (IOP), and the fixed-combination medications are needed to achieve sufficiently low target IOP. The aim of this systematic review and meta-analysis is to evaluate IOP-lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol.

Methods: Pertinent publications were identified through systematic searches. Over 85% of the patients had to be diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). Forty-one randomized clinical trials were included in the meta-analysis. The main efficacy measures were the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP reductions on the diurnal IOP curve. The pooled 1- to 3-month IOP-lowering effects after a medicine-free washout period was calculated by performing meta-analysis using the random effects model, and relative treatment effects among different fixed combinations were assessed using a mixed-effects meta-regression model.

Results: The relative reductions for mean diurnal IOP were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. For the highest IOP decrease, relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol; for the lowest IOP decrease, those varied from 25.9% for dorzolamide/timolol to 33.1% for bimatoprost/timolol. Both latanoprost/timolol and travoprost/timolol were more effective in lowering mean diurnal IOP than brimonidine/timolol (WMD: 5.9 and 7.0) and dorzolamide/timolol (WMD: 3.8 and 3.3).

Conclusions: All six commonly used fixed-combination drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.