Therapeutic Class Overview
Ophthalmic Agents, Intraocular Pressure (IOP)-Modifying

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, and in 2020, an estimated 3.2 million people worldwide are anticipated to be blind due to glaucoma (*Flaxman et al 2017*). Open-angle glaucoma is the most common form; other forms include angle-closure, congenital, and secondary glaucoma *(Jacobs 2018[a])*. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated *(Jacobs 2018[a])*. The exact etiology of open-angle glaucoma is unknown *(Jacobs 2018[a])*. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia *(Ellis et al 2000, Girkin et al 2004, Lesk et al 2007, Prum et al 2016)*.
- Elevated IOP is the only major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage *(Jacobs 2018[a])*. Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage *(Jacobs 2018[a])*. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression *(Jacobs 2018[b])*. The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life *(Jacobs 2018[b])*. The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented *(Prum et al 2016)*.
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. Medical intervention is generally used as initial therapy prior to laser or surgical treatment *(Jacobs 2018[b])*. Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors *(Jacobs 2018[b], Micromedex 2019)*. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow *(Micromedex 2019, Prum et al 2016)*. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production *(Micromedex 2019)*. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow *(Micromedex 2019, Prum et al 2016)*.
- Guidelines published in 2010 by the American Optometric Association (AOA) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents *(Jacobs 2018[b])*.
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03% and indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator. Latisse is included here for informational purposes since it contains the same ingredient used for the reduction of elevated IOP.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1% and 0.15% *	✔ †

Drug	Generic Availability
brimonidine tartrate ophthalmic solution 0.2% ‡	✔
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
Betagan (levobunolol hydrochloride ophthalmic solution) 0.25% and 0.5%	✔
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	✔
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
metipranolol ophthalmic solution 0.3% **	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	-
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Phospholine Iodide (echothiophate iodide for ophthalmic solution) 0.125%	-
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%	✔
Prostaglandin Analogues	
bimatoprost ophthalmic solution 0.03%	✔
Latisse (bimatoprost ophthalmic solution) 0.03%	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% ††	-
Travatan Z (travoprost ophthalmic solution) 0.004% ‡‡	-
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	-
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	-
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
† The Alphagan P 0.15% strength is available generically; however, the 0.1% strength is only available as a branded product.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is only available as a branded product only.
‖. Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
** Brand OptiPranolol is no longer available.
†† Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
‡‡ The original benzalkonium chloride-containing travoprost formulation (brand name: Travatan) was approved by the FDA on March 16, 2001; however, Travatan was discontinued by Alcon in June 2010. In March 2013, travoprost with benzalkonium chloride by Par Pharmaceuticals was approved by an abbreviated new drug application (ANDA); however, this generic product was discontinued on September 7, 2016 *(Clinical Pharmacology 2019)*. Only the brand product, Travatan Z, remains available.

(DRUGS@FDA.com 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate) *	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betagan (levobunolol)	✔ ‡			
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol	✔ ‡			
Istalol (timolol maleate)	✔			
metipranolol	✔			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
brinzolamide	✔			
dorzolamide	✔			
Prostaglandin Analogues				
latanoprost	✔			
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				
Rhopressa (netarsudil)	✔			
Combinations				

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Combigan (brimonidine/timolol) ‖				✔
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(Prescribing information: Alphagan P 2013, Azopt 2015, Betagan 2017, betaxolol hydrochloride ophthalmic solution 2017, Betimol 2017, Betoptic S 2018, bimatoprost ophthalmic solution 0.03% 2017, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2016, Combigan 2015, Cosopt 2018, Cosopt PF 2017, Iopidine 0.5% 2018, Iopidine 1% 2018, Istalol 2016, Latisse 2017, Lumigan 2017, metipranolol ophthalmic solution 2011, Rhopressa 2017, Simbrinza 2015, Timoptic 2016, Timoptic in Ocudose 2017, Timoptic-XE 2018, Travatan Z 2017, Trusopt 2014, Vyzulta 2018, Xalatan 2017, Xelpros 2018, Zioptan 2018)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Accommodative esotropia	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Reduction of elevated IOP
Miotics						
Isopto Carpine (pilocarpine)	✔		✔	✔	✔	
Phospholine Iodide (echothiophate iodide)		✔				✔

(Prescribing information: Isopto Carpine 2010, Phospholine Iodide 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient reported outcomes, or visual impairment. Very little direct comparative evidence is available *(Boland et al 2012, Boland et al 2013)*.
- A network meta-analysis included 114 randomized controlled trials (n = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma *(Li et al 2016)*. All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62) (currently not available in U.S.), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67) (currently not available in the U.S.). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- A network meta-analysis evaluated 72 randomized controlled trials (n = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia with the exception of the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (n = 6841) and trough (n = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol *(Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008)*. Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6 week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3 month study *(Coleman et al 2003)*. However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy *(Barnes et al 1999, Chen et al 2001, Chen et al 2005, Sterk et al 1998)*.

- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% ($p \leq 0.025$). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% ($p = 0.014$). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient ($p < 0.001$) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (n = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma *(Zhang et al 2017)*. Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs apraclonidine (3 randomized controlled trials), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether 1 medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Boozman et al 1988, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mills et al 1986, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline *(Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989)*.
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) *(Vogel et al 1989)*.
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP *(Berry et al 1984, Stewart et al 1986)*.
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant *(Berry et al 1984, Vogel et al 1989)*.
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) *(Watson et al 2001)*.

- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% *(Berson et al 1985, Boozman et al 1988, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998)*.
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) *(Krieglstein et al 1987)*.
  - When levobunolol 0.25% was compared to timolol maleate 0.25%, the mean changes in IOP from baseline to 48 weeks were reported as -5.1 mmHg in the levobunolol 0.25% group and -4.6 mmHg in the timolol maleate 0.25% group (p value not reported) *(Boozman et al 1988)*.
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event ($p = 0.024$). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group ($p < 0.001$) *(Halper et al 2002)*.
- One study compared metipranolol 0.3% to timolol 0.25% and found that both treatments significantly decreased IOP from baseline. There was a larger reduction in IOP in the metipranolol 0.3% group; however, the difference was not found to be statistically significant (p value not reported) *(Mills et al 1986)*.
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) *(Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002)*. The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% ($p < 0.05$) and also caused more stinging and burning ($p = 0.001$) *(Mundorf et al 2004)*.
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing ($p = 0.04$ for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS ($p = 0.04$). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment ($p = 0.024$); however, this was not found to be significant at 24 weeks of treatment *(Shedden et al 2001)*.

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect *(Cantor et al 2001, Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver et al 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004)*.
  - In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
  - Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*March et al 2000, Varma et al 2009, Haneda et al 2006*).
  - In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) *(Walters et al 2004)*.
  - In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) *(Ikeda et al 2008)*.

Carbonic Anhydrase Inhibitors

- Trials support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide. The trials evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2015* and *Trusopt prescribing information 2014).* However, the efficacy of ophthalmic carbonic anhydrase inhibitors in reducing vision loss due to glaucoma has not been established in clinical trials (*Jacobs 2018[b]*).

- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) *(Silver 1998).* In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event *(Silver 2000).*
- Similar reductions in IOP were also observed when the agents were used in combination with timolol *(Michaud et al 2001).*

Carbonic Anhydrase Inhibitors compared to other classes

- The single agent carbonic anhydrase inhibitors were compared to beta-blockers *(March et al 2000, Rusk et al 1998, Strahlman et al 1995)*. Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel group, randomized controlled trial, timolol was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily ($p = 0.0002$) *(March et al 2000).*
  - When dorzolamide was compared to betaxolol or timolol in a 1 year, double-blind, parallel group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) *(Strahlman et al 1995)*.
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) *(Rusk et al 1998).*
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy ($p < 0.001$ for both groups) *(Bournias et al 2009)*.

Miotics

- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics are very limited. These agents have been available for many years and are recognized as an established treatment option (*Prum et al 2016*). No clinical trials have been published in the last 30 years on echothiophate iodide.

Miotics compared to other drug classes

- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues *(Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999).* A trial has evaluated pilocarpine plus a beta-blocker and found that pilocarpine is an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues *(Diestelhorst et al 2000).*
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery *(Ren et al 1999).*

Prostaglandin Analogues

- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost *(Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012)*.
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72), and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk *(Lin et al 2014)*.
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM ($p = 0.004$) and 12 noon ($p = 0.02$), but not at 4 PM ($p = 0.19$) or 9 PM ($p = 0.07$). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at

all time points. There were no statistically significant differences between latanoprost and travoprost at any time point *(Aptel et al 2008)*.
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patents with open-angle glaucoma or ocular hypertension *(Li et al 2006)*.
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) *(Honrubia et al 2009)*.
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data has not been included in many meta-analyses. Available trials suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost *(Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010[b])*.
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) *(Traverso et al 2010)*.
  - In a 6 week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups *(Schnober et al 2010)*.
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments *(Uusitalo et al 2010[b])*.
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; p = 0.049) *(Uusitalo et al 2010[a])*.
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) *(Chabi et al 2012)*.
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; N = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016*, *Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28 day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% *(Weinreb et al 2015)*.
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in 3 Phase 3, randomized, double-masked, active control, parallel group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and at 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points *(Rhopressa FDA Medical Review, Rhopressa Prescribing Information 2017, Serle et al 2018)*.

- Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
- In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Rhopressa FDA Medical Review, Serle et al 2018)*.
- In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Rhopressa FDA Medical Review, Serle et al 2018)*.
- In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 30 mmHg in the per-protocol (PP) population, but this result was not replicated in the intent-to-treat (ITT) population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 25 mmHg in both PP and ITT populations (*Rhopressa FDA Medical Review).*

- Netarsudil was also evaluated in a 28 day, Phase 2, dose-response, double-masked, active control, parallel group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline *(Craven et al 2005, Goñi et al 2005, Sherwood et al 2006)*. In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study *(Katz et al 2012)*. The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to 2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.
- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3 month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group *(Katz et al 2013, Nguyen et al 2013, Realini et al 2013)*.
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months *(Whitson et al 2013)*. Another trial evaluating twice daily dosing was conducted after the US approval of the thrice daily dosing. Results were similar to those previously observed *(Aung et al 2014)*.
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks *(Kozobolis et al 2017)*.

- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment *(Clineschmidt et al 1998)*.

- One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation *(Renieri et al 2010).* Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.

- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) *(Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012)*. However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; p = 0.03) *(Garcia-Feijoo et al 2010)*. In a crossover study of 77 patients, 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 mmHg; 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) *(Konstas et al 2012)*. It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)

- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Prum et al 2016)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, and they are relatively safe. They are, therefore, often considered as initial medical therapy unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

AAO – Esotropia and Exotropia Preferred Practice Pattern (*AAO 2017*)

- Guidelines for esotropia and exotropia from the AAO note that cholinesterase inhibitors such as echothiophate iodide reduce accommodative effort and convergence by stimulating ciliary muscle contraction (*AAO 2017*). Echothiophate iodide is among several treatment options that also include corrective lenses, bifocals, prism therapy, botulinum toxin injection, and extraocular muscle surgery.
  - Echothiophate iodide, in the long term, is less desirable than using corrective lenses because of systemic adverse effects such as diarrhea, asthma, and/or increased salivation and perspiration.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
  - Echothiophate iodide is contraindicated in acute uveitis, angle-closure glaucoma, and in patients with known hypersensitivity to echothiophate iodide or any component of the formulation.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entity or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.
    - Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including funduscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
    - Caution is advised when administering ophthalmic pilocarpine solution for control of IOP in pediatric patients with primary congenital glaucoma.
    - Caution should be exercised when administering echothiophate iodide in patients with disorders that may respond adversely due to the potential for vagotonic effects.
    - Great caution should be used when administering other cholinesterase inhibitors (ie, succinylcholine), or with exposure to organophosphate or carbamate insecticides, at any time in patients receiving anticholinesterase medications including echothiophate iodide. Respiratory or cardiovascular collapse may occur. Use caution when treating glaucoma with echothiophate iodide in patients receiving systemic anticholinesterase medications for myasthenia gravis due to the risk of possible additive effects. Patients with active or a history of quiescent uveitis should consider avoiding echothiophate iodide. If used with caution, there is a potential for intense and persistent miosis and ciliary muscle contraction.
    - If cardiac irregularities occur with echothiophate iodide use, temporary or permanent discontinuation is recommended.
    - If salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, or respiratory difficulties occur with echothiophate iodide use, temporary discontinuation of the medication is recommended.
  - Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.

- ROCK inhibitor
  - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
- Adverse reactions
  - Alpha-Agonists
    - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
    - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
    - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
  - Beta-blockers
    - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
  - Carbonic Anhydrase Inhibitors
    - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
    - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste which have been reported in up to 30% of patients.
  - Miotics
    - Most adverse events reported with the miotics are associated with the eye. Visual blurring, burning, eye irritation, and eye pain have been reported.
  - Prostaglandin Analogues
    - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
  - ROCK inhibitor
    - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
      - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.
- Drug interactions
  - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.
  - Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
Betagan (levobunolol)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by strength)	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy: Unclassified†
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy Category C‡
metipranolol	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy Category C‡
Carbonic Anhydrase Inhibitors				
brinzolamide	Ophthalmic suspension	Ophthalmic	Three times daily	A 3 month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy Category C‡
dorzolamide	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy Category C‡
Miotics				
Phospholine Iodide (echothiophate iodide)	Ophthalmic powder for reconstitution	Ophthalmic	Once or twice daily Chronic open-angle glaucoma:	Requires reconstitution. Store reconstituted solution at room temperature and discard any unused solution after 4 weeks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Twice daily; may be used once daily or once every other day Accommodative esotropia: Daily or every other day	Pregnancy: Unclassified†
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30 minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Prostaglandin Analogues				
latanoprost	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Latisse (bimatoprost)	Ophthalmic solution	Ophthalmic	Daily	May be used in patients aged ≥ 5 years for hypotrichosis of the eyelashes. Bimatoprost has been studied in patients aged 5 to 17 years who were post-chemotherapy or had alopecia and ages 15 to 17 years with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				hypotrichosis not associated with a medical condition. Pregnancy: Unclassified†
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion Xelpros is preservative-free swollen micelle microemulsion.	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to 16 years of age; contraindicated in pediatric

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				patients < 2 years. Pregnancy: Unclassified†
Cosopt / Cosopt PF (dorzolamide /timolol)	Ophthalmic solution Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy Category C‡
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
† In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡ Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. There are no standard guidelines for a target IOP (*Jacobs 2018[b]*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class,

although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory *(AOA 2010, Prum et al 2016)*. Combination therapy can be given as separate drops or in fixed dose combinations which include brimonidine/timolol, brimonidine/brinzolamide, and dorzolamide/timolol.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Jacobs 2018[b]*).
  - The AAO and AOA guidelines have not been updated to include Xelpros (latanoprost ophthalmic emulsion) or Vyzulta (latanoprostene bunod). A corrigendum to the 2016 AAO guidelines was issued in 2018 to acknowledge the use of ROCK inhibitors for reduction of IOP; no specific agents are mentioned in the update.
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues *(Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018)*.
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma *(Jacobs 2018[b])*.
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction. Ophthalmic pilocarpine is indicated for control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Echothiophate iodide is indicated for chronic open-angle glaucoma and accommodative esotropia. The ophthalmic miotics are an established treatment option as they have been available since the 1960s.

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