Optimizing Topical management of Glaucoma

Pinakin Davey OD, PhD, FAAO, FARVO
Professor and Director of Clinical Research
Western University of Health Sciences
Pomona California

1

Disclosure

- Thea Pharma Consultant
- Sanofi Speaker
- Innova System Consultant
- EyePromise Employee

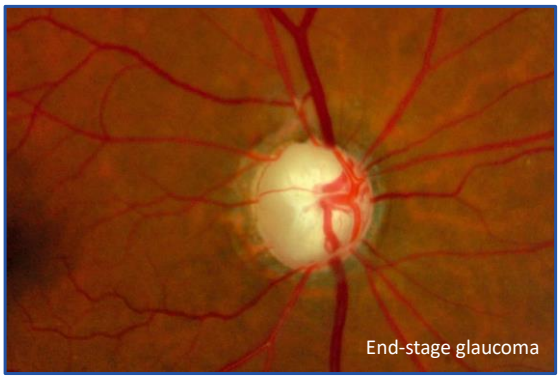
The content and format of this course is presented without commercial bias and does not claim superiority and commercial product or service.

"All relevant financial relationships have been mitigated"

2

Glaucoma Overview

- Group of ocular disease- Progression
  - Can damage optic nerve and lead to vision loss if left untreated[a]
    - Leading cause of irreversible vision loss
    - Second leading cause of preventable blindness, after cataracts[b]
- Asymptomatic until later stages, when significant and irreversible visual impairment has already taken place[c]
- Up to 50% of all glaucoma cases remain undiagnosed[c]



a. CDC. Vision Health Initiative. Reviewed November 24, 2020. Accessed May 15, 2023; b. Pereira ICF, et al. Eye. 2021;35:3202-3221; c. Tapply I, et al. Patient Prefer Adher. 2021;15:1477-1489. Image by Philippin H, et al. Community Eye Health Journal. 2012;25:82.

3

Glaucoma Prevalence and Risk Factors

- > 70 million people worldwide have glaucoma[a]
- Includes ~3 million Americans[b]

Glaucoma can affect anyone, but certain groups are at higher risk!

Patients at higher risk for glaucoma[a]

- All people aged > 60 yr
- Black people aged > 40 yr
  - 6 to 8 times higher risk vs White counterparts
- People with a family history of glaucoma
- People with diabetes
  - Risk doubled vs individuals without diabetes

a. Pereira ICF, et al. Eye. 2021;35:3202-3221; b. CDC. Vision Health Initiative. Reviewed November 24, 2020. Accessed May 15, 2023.

4

Setting Intraocular Pressure (IOP) Target Ranges

5

Ocular hypertension Overview

Patients with OH are considered "glaucoma suspects"

- Occurs when anterior portion of the eye is unable to properly drain fluid
  - Results in increased IOP
- **Prevalence of 3-4% in general population**
  - **Reaches 8% in people aged ≥ 80 yr**
- Increases risk for glaucoma
- Clinically, optic nerves look normal and there is no vision loss

Boyd K; American Academy of Ophthalmology. Eye Smart. Published 2022. Accessed May 15, 2023; Saboo US, et al. Graefes Arch Clin Exp Ophthalmol. 2016;254:923-928.

6

The Scoring Tool for Assessing Risk (S.T.A.R. II) calculator

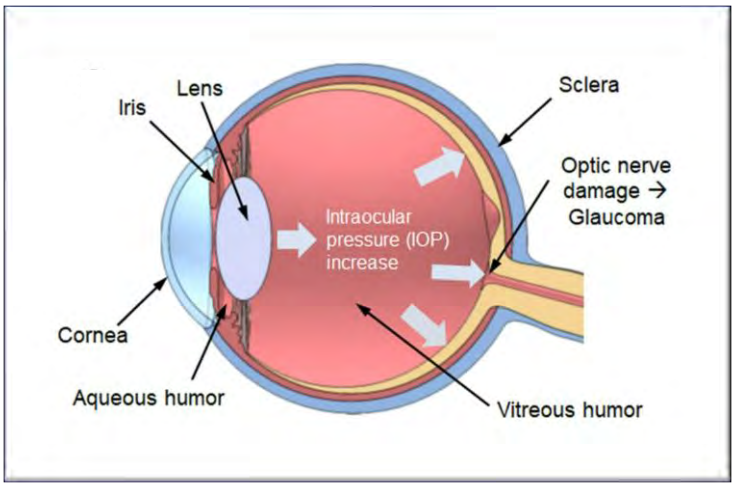
- OHTs and EGPS data
- Intended for use only in untreated OHT patients
- Age (30-80)
- IOP 20-32 mmHg
- CCT 475 to 650 microns
- PSD 0.50 to 3.00 dB
- C/D ratio vertical 0.00 to 0.8

Probability of conversion in 5- years
<5% observe and monitor
5 to 15% consider treatment
>15% treat

https://ohts.wustl.edu/risk/

7

Intraocular pressure



Overview[a,b]

- Imbalance between production and drainage of aqueous humor
- IOP > 21 mm Hg is considered elevated
  - Most important known risk factor for OH and POAG
- All current treatments target IOP levels
- Patients with POAG should be offered lifelong control of IOP
  - Require monitoring of optic nerve appearance and visual function

a. Tapply I, et al. Patient Prefer Adher. 2021;15:1477-1489; b. Pereira ICF, et al. Eye. 2021;35:3202-3221.
Image by Kim Y, et al. Scientific Reports. 2019;9:15215.

8

Staging POAG

Stage/Severity	Symptoms/Signs
1 – Suspected	✓ IOP ≥ 22 mm Hg ✓ Asymmetry of vertical C/D ratio (> 0.2 between the 2 eyes) ✓ Suspect appearance of the optic disc ✓ Suspected central-field defect
2 – Mild (early)	✓ Slight glaucomatous changes in the cup (C/D ratio ≤ 0.65 for an optic nerve of average diameter) ✓ Slight visual-field defect outside the central 10°
3 – Moderate	✓ Moderate glaucomatous changes in the cup (C/D ratio 0.7-0.85) ✓ Moderate visual-field defect outside the central 10°
4 – Advanced	✓ Significant glaucomatous changes in the cup (C/D ratio ≥ 0.9) ✓ Visual-field defect within the central 10°

C/D, cup/disc.

Fontaine N, et al. Semantic Scholar. Published 2013. Accessed June 6, 2023.

9

IOP Target Ranges

	Glaucoma Severity		
	Mild	**Moderate**	**Advanced**
Target range	High teens	Mid teens	Low teens
Acceptable fluctuation	< 5 mm Hg	< 4 mm Hg	< 3 mm Hg*

*Least fluctuation tolerance

Asrani S. Rev Ophthalmol. Published 2016. Accessed May 15, 2023.

10

Examining Eye Drops for Glaucoma

11

Prescription Eye Drops: A Popular Solution

- Most common treatment for glaucoma
- Used daily, with dosing frequency from 1-4 times daily
- Cannot cure glaucoma or reverse vision loss but can slow or stop progression
- Lower IOP, thereby preventing damage to optic nerve

IOP-Lowering Mechanism of Action

1 of 2 strategies:

1. Drain excess ocular fluid (ie, aqueous humor)
2. Lower production of aqueous humor

7 types of eye drops are available to treat OH and POAG

National Eye Institute. Published 2021. Accessed May 15, 2023. https://www.nei.nih.gov/Glaucoma/glaucoma-medicines
Image produced by DALL-E, https://labs.openai.com/

12

FDA-Approved Eye Drops

Drain excess aqueous humor	
Prostaglandin analogs (PGAs)*	Latanoprost, travoprost, tafluprost, bimatoprost, latanoprostene bunod, omidenepag isopropyl (Not available)
Rho kinase inhibitors	Netarsudil
Cholinergic or mitotic agents	Pilocarpine, carbachol (rarely considered)
Lower production of aqueous humor	
Alpha-adrenergic antagonists	Apraclonidine, brimonidine
Beta blockers	Betaxolol, timolol
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide

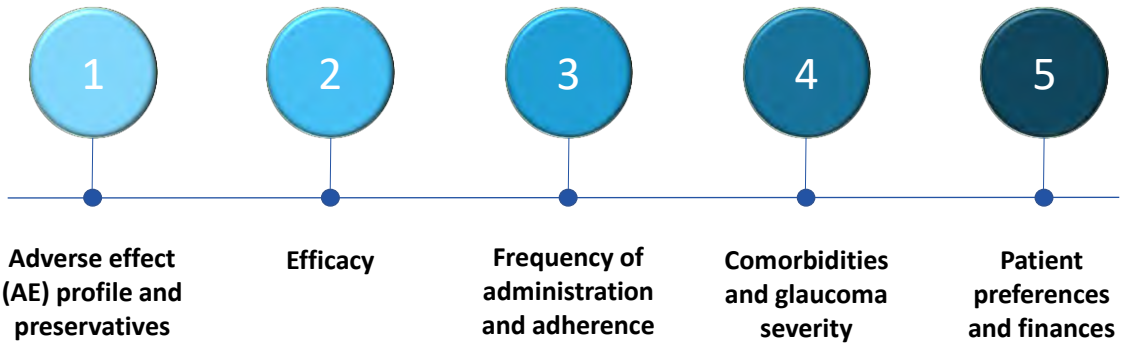
*Includes first-generation agents, NO-donating agents, and EP2 receptor agonists.

EP2, prostaglandin E receptor 2; NO, nitric oxide.

National Eye Institute. Published 2021. Accessed May 15, 2023. https://www.nei.nih.gov/Glaucoma/glaucoma-medicines

13

Selecting Eye Drops: Factors to Consider



Even eye drops within the same medication class have noticeable differences, making it important for clinicians to understand the distinctions, whether using them as a monotherapy or in combinations

AAO and AGS. Statement on Glaucoma Eye Drop Availability. Published 2014. Accessed May 15, 2023.

14

Prostaglandin Analogues (PGAs)

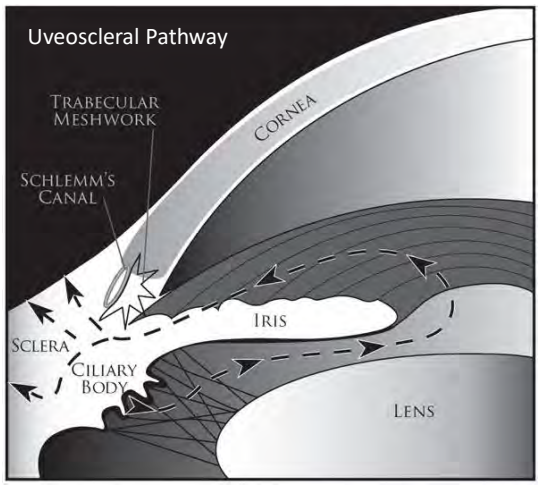
15

PGAs and Uveoscleral Outflow

PGAs primarily affect uveoscleral outflow (unconventional pathway)

Uveoscleral outflow accounts for 20% to 40% of the total aqueous humor drainage from the eye

PGAs cause aqueous humor to move through the interstitial spaces of the ciliary muscle into the suprachoroidal space of eye, where the humor drains into the ciliary body capillaries and lymphatic vessels



Impagnatiello F, et al. Br J Pharmacol. 2019;176:1079-1089.
Image by Goel M, et al. The Open Ophthalmology Journal. 2010;4:52-59.

16

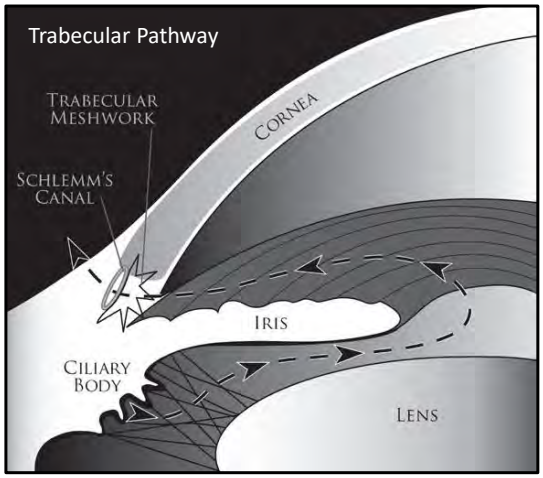
PGAs and Trabecular Outflow

PGAs have been more recently identified to also drain ocular fluid via trabecular outflow

Trabecular outflow accounts for 70% to 90% of total aqueous humor drainage from the eye

Numerous PGA effects may contribute to aqueous humor outflow via the trabecular pathway

- Loss of extracellular matrix from the juxtacanalicular region and cell disconnection from the extracellular matrix
- EP receptor stimulation, alters cell contractility of the trabecular meshwork
- Altered production of MMPs



EP, E-prostanoid; MMPs, matrix metalloproteinases.
Winkler NS, et al. J Ocul Pharmacol Ther. 2014;30:102-109.
Image by Goel M, et al. The Open Ophthalmology Journal. 2010;4:52-59.

17

How PGAs Work

PGAs mimic the function of naturally occurring prostaglandins

- Prostaglandins are pro-inflammatory molecules that bind to receptors throughout entire body
  - 4 principal bioactive prostaglandins are generated in vivo: PGE2, PGI2, PGD2, and PGF2α

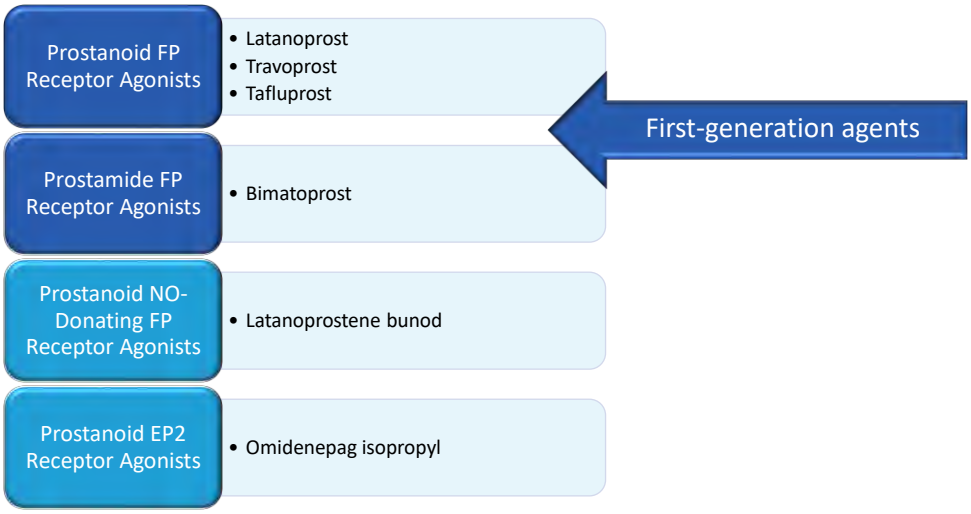
FP receptors have been conventionally targeted in glaucoma treatment, but EP receptor agonists are emerging[b]

- **FP receptors:** Increase MMP enzymes in ciliary muscle and surrounding tissue that dissolve collagenase types I and III, promoting rearrangements of the ciliary muscle and sclera that favor more efficient uveoscleral drainage of aqueous humor
- **EP receptors:** Widely expressed in the trabecular meshwork, Schlemm's canal endothelium, and ciliary muscles, thereby affecting aqueous humor outflow via conventional and unconventional pathways

FP, prostaglandin F receptor.

18

FDA-Approved PGAs



.

19

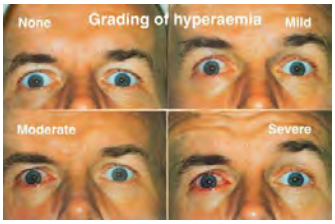
PGAs: Benefits and Issues

Benefits
- Highly effective
- Once-daily dosing makes them an ideal choice for monotherapy
- Limited AE profile
  - Most common AEs are conjunctival hyperemia and inflammation
  - No systemic effects

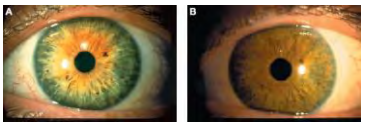
Issues
- Responsiveness to PGAs can be highly variable
- Non responders
- Side effects

20

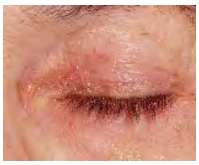
F2 alpha Prostaglandin related side effects



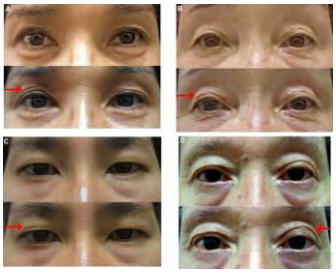
Hyperemia



Iris color changes



Eye lash growth
Pigmentary changes



DUES or Prostaglandin associate periorbitopathy

21

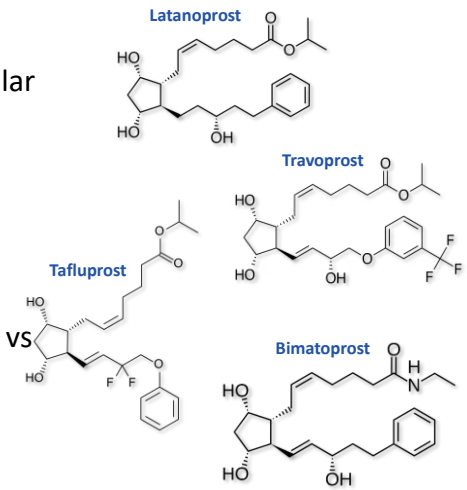
First-Generation PGAs: Efficacy

RCT of 60 patients with newly diagnosed glaucoma[a]

- Latanoprost, travoprost, and tafluprost showed similar efficacy in reducing mean IOP levels and controlling diurnal IOP fluctuations[a]

Meta-analysis of 17 studies[b]

- Latanoprost and travoprost showed comparable IOP reductions
- Bimatoprost slightly more effectively controlled IOP vs latanoprost or travoprost with longer and more continued use (≥ 3 months)



a. Faseeh AE, et al. Eur J Ophthalmol. 2021;31:3018-3026; b. Tang W, et al. Medicine (Baltimore). 2019;98:e16597.

22

First-Generation PGAs: Safety

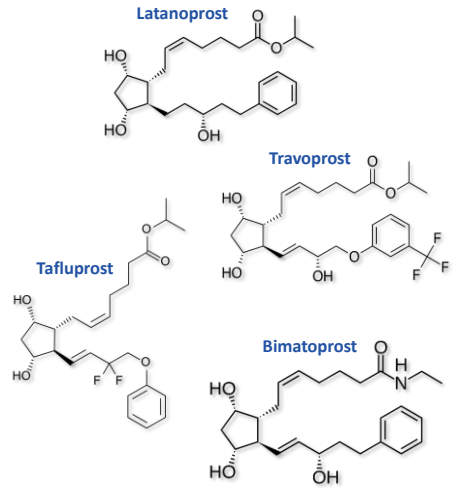
RCT of 60 patients with newly diagnosed glaucoma[a]

- No significant differences in AE patterns between latanoprost, travoprost, and tafluprost

Meta-analysis of 17 studies[b]

- Latanoprost was best tolerated
  - Lower risk of conjunctival hyperemia and lash growth vs travoprost
- Bimatoprost had lower ocular tolerability and a higher incidence of conjunctival hyperemia vs travoprost

Differences in efficacy and safety may be explained by factors such as varying affinity for targeted receptors and use of different concentrations and formulas (prostanoid vs prostamide)



a. Faseeh AE, et al. Eur J Ophthalmol. 2021;31:3018-3026; b. Tang W, et al. Medicine (Baltimore). 2019;98:e16597.

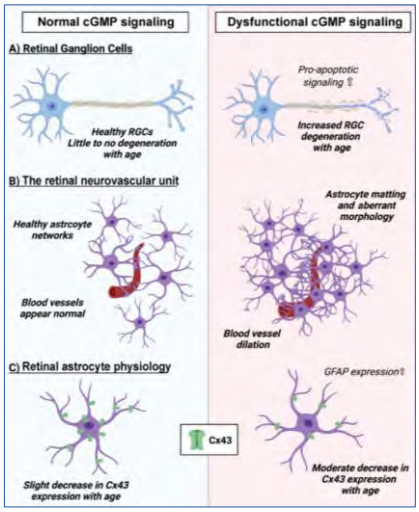
23

A Discussion of first generation PGA agents

When, How and Why?

24

NO-Donating FP Receptor Agonists: Overview



- NO and its second messenger cGMP are important in IOP regulation[a,b]
- NO-donating PGAs lower IOP via unconventional and conventional pathways[c]
  - Enhanced uveoscleral outflow via FP receptor activation
  - Greater trabecular meshwork outflow via cGMP stimulation
- Latanoprostene bunod 0.024% (LBN) became first FDA-approved NO-donating PGA in 2017[a]

cGMP, cyclic guanosine monophosphate.

a. Impagnatiello F, et al. Br J Pharmacol. 2019;176:1079-1089; b. Holden JM, et al. Neural Regen Res. 2023;18:1267-1268; c. Kaufman PL. Expert Opin Pharmacother. 2017;18:433-444.
Image from Holden JM, et al. Neural Regen Res. 2023;18:1267-1268.

25

Latanoprostene Bunod: Efficacy and Safety

- Efficacy and safety established in APOLLO and LUNAR phase 3 trials and single-arm JUPITER study[a-c]

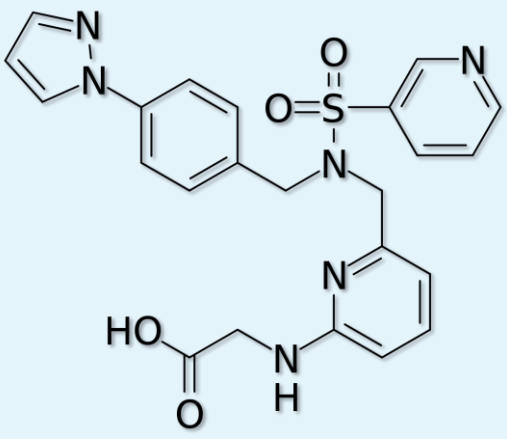
APOLLO[a]	LUNAR[b]	JUPITER[c]
Efficacy: **IOP was significantly lower** in the LBN vs timolol group at **all 9 timepoints** assessed: 8 AM, 12 PM, and 4 PM on week 2, week 6, and month 3 visit **Safety:** **Similar safety** across arms, with most being **mild or moderate**; AEs in ≥ 1% of eyes included eye irritation, conjunctival hyperemia, eye pain, dry eye, and instillation site pain	**Efficacy:** Mean **IOP reduction was significantly greater with LBN** vs timolol at all but 1 timepoint assessed; 31.0% LBN vs 18.5% timolol had IOP reductions ≥ 25% from baseline, and 17.7% vs 11.1%, respectively, had their IOP reduced to ≤ 18 mm Hg over all time points/visits **Safety:** **Ocular AEs were uncommon**; more frequent with LBN (all were mild/moderated except 1 case of severe hyperemia); most common AEs with LBN included conjunctival hyperemia, eye irritation, and eye pain	**Efficacy:** Mean reductions from baseline in IOP of 22.0% and 19.5% were achieved by week 4 in study and treated fellow eyes, respectively, with **IOP reductions maintained through week 52** **Safety:** Most common AEs in study and treated fellow eyes were **conjunctival hyperemia** (~17%), **growth of eyelashes** (~16%), **eye irritation** (~11%), and **eye pain** (~10%)

LBN, latanoprostene bunod.

a. Weinreb RN, et al. Ophthalmology. 2016;123:965-973; b. Medeiros FA, et al. Am J Ophthalmol. 2016;168:250-259; c. Kawase K, et al. Adv Ther. 2016;33:1612-1627.

26

EP2 Receptor Agonists: OMDI



First FDA approval[a]
- Approved September 2022
- First FDA-approved EP2 receptor agonist for OAG and OH

New mechanism of action[b]
- Isopropyl ester prodrug
- Undergoes hydrolysis to omidenepag, its active metabolite, during corneal penetration
- Behaves as a nonprostaglandin, selective EP2 receptor agonist

Uses unconventional and conventional drainage
- Increases aqueous humor drainage through uveoscleral and trabecular pathways via its effects on cAMP[b,c]

a. Koury C. Glaucoma Physician. Published December 1, 2022. Accessed May 15, 2023; b. Matsuo M, et al. Clin Ophthalmol. 2022;16:1261-1279; c. Elhusseiny AM, et al. AAO. Updated April 2, 2023. Accessed May 15, 2023.

27

OMDI 0.002%: Efficacy and Safety

- Efficacy and safety were established in the AYAME and RENGE phase 3 RCTs and the phase 3 open-label FUJI study[a-c]

AYAME[a]	RENGE[b]	FUJI[c]
Efficacy: IOP was lowered from a mean of **23.78 ± 1.73 at baseline to 17.81 ± 2.41 at week 4** in the OMDI arm and from 23.40 ± 1.51 mm Hg at baseline to 16.96 ± 2.24 mm Hg at week 4 in the latanoprost arm **Safety:** **No serious AEs** occurred in either arm; the most common ocular AEs included conjunctival hyperemia (25.4% OMDI vs 10.4% latanoprost), corneal thickening (11.7% vs 1.0%, respectively), and punctate keratitis (0% vs 5.2%, respectively)	**Efficacy:** Mean IOP reductions of **-3.7 ± 0.3 mm Hg** (cohort 1), **-5.6 ± 0.5 mm Hg** (cohort 2), and **-8.4 ± 0.6 mm Hg** (cohort 3) at 52 weeks* **Safety:** **Most AEs were mild**, with no serious AEs reported; most frequent AEs included conjunctival hyperemia (18.8%, monotherapy cohorts; 45.0% combination cohorts) and macular edema/cystoid edema (11.8%, monotherapy; 15.0% combination)	**Efficacy:** Mean diurnal IOP was lowered from mean of 25.00 ± 2.66 mm Hg at end of latanoprost washout period to **23.12 ± 2.80 mm Hg after 4 weeks of OMDI treatment** **Safety:** **Mild to moderate AEs occurred in 19.2% of patients**, with no severe AEs observed; ocular AEs included anterior chamber cells (7.7%), conjunctival hyperemia (7.7%), erythema of eyelid (3.8%), and retinal hemorrhage (3.8%)

*Cohort 1, baseline diurnal IOP ≥ 16 to < 22 mmHg, treated with OMDI once daily; Cohorts 2 and 3, baseline diurnal IOP ≥ 22 to ≤ 34 mm Hg treated with OMDI once daily or OMDI once daily plus timolol 0.5% twice daily, respectively

a. Aihara M, et al. Am J Ophthalmol. 2020;220:53-63; b. Aihara M, et al. Jpn J Ophthalmol. 2021;65:810-819; c. Aihara M, et al. Jpn J Ophthalmol. 2020;64:398-406.

28

EP receptor agents- A Discussion

When to use these drugs ?
What can one expect?

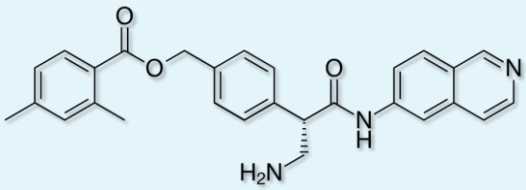
29

Other Drops Draining Excess Aqueous Humor

30

ROCK Inhibitors: Netarsudil 0.02%

Relatively new class of drug for use in glaucoma



FDA approval in 2017[a]
- Indicated to reduce elevated IOP in patients with OH and OAG

Lowers IOP by inhibiting both ROCK and NET[b]
- ROCK inhibition enhances trabecular outflow and reduces episcleral venous pressure
- NET inhibition decreases aqueous humor production

Once-daily dosing[a]
- Instilled in the evening

NET, norepinephrine transporter; OAG, open-angle glaucoma; ROCK, rho kinase.
a. Patel P, et al. StatPearls. Updated November 24, 2023. Accessed May 15, 2023; b. Serle JB. Glaucoma Today. Published September/October 2017. Accessed May 15, 2023.

31

Netarsudil: Efficacy and Safety

Efficacy

Meta-analyses
- Hypotensive effect of netarsudil monotherapy possibly inferior to latanoprost and slightly inferior to timolol[a]
  - IOP lowering increased when netarsudil was combined with latanoprost
- Review of ROCK inhibitor trials suggests IOP reductions **comparable to timolol**[b]

Real-World Study
- Netarsudil monotherapy resulted in an IOP reduction of ~3 mm Hg from baseline[c]

Safety

- Treatment is **generally well tolerated**[a-c]
  - AEs mild to moderate
- Most frequently reported AEs include:[b]
  - Conjunctival hyperemia (19-65%)
  - Conjunctival hemorrhage (6-20%)
  - Cornea verticillata (13-26%)
- Netarsudil as a monotherapy or in combination may result in **more ocular AEs** vs first-generation PGAs[a]

a. Clement Freiberg J, et al. Cochrane Database Syst Rev. 2022;6(6):CD013817; b. Wu JH, et al. Graefes Arch Clin Exp Ophthalmol. 2022;260:937-948;
c. Fridman G, et al. J Ocul Pharmacol Ther. 2021;37:338-342.

32

Cholinergic (Miotic) Agents

Oldest effective medical treatment for glaucoma

- Used since 1870s

May reduce IOP by 17% to 25%

- Constrict the pupillary sphincter, tighten the iris, decrease volume of iris tissue in the angle, and pull the peripheral iris away from the trabecular meshwork
  - Enables aqueous humor to reach the outflow channels

May be used alone or as a combination therapy

- Monotherapy ineffective when significantly elevated IOP (ie, 40-45 mm Hg)
  - Due to a higher likelihood of an ischemic pupillary sphincter

Used more rarely due to toxicity concerns and availability of more effective/better tolerated agents

- Tolerability issues (eg, dimmed vision, especially at night; headaches)
- Risk of more severe ocular AEs (eg, uveitis, retinal detachment/tear)
- Contraindications to use (eg, asthma, iritis)

33

ROCK Inhibitors and Cholinergic Agents - A Discussion

When and why?

34

Eye Drops That Reduce Fluid Production

35

Topical Beta Blockers

Used for many decades to treat glaucoma[a]

- First agent, timolol, was approved in 1979

Reduce IOP by blocking sympathetic nerve endings in the ciliary epithelium[b,c]

- Limits active transport and production of aqueous humor

Two types of topical beta-blockers are available[c]

- Nonselective: Block beta 1- and beta 2-adrenoceptors
  - Includes **timolol**, metipranolol, and carteolol
- Cardioselective: Block only beta 1-receptors
  - Only **betaxolol**

Can be administered once or twice daily[c]

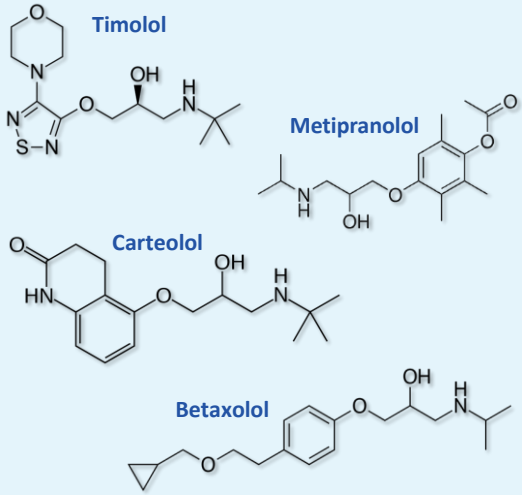
- Aqueous solutions and gel formulations are available

Second most often used class of medication for glaucoma

a. Karmel M, et al. EyeNet Magazine. Published March 2009. Accessed May 11, 2023; b. Negri L, et al. J Ophthalmol. 2019;2019:4146124; c. Brooks AM, et al. Drugs Aging. 1992;2:208-221.

36

Beta Blockers: Efficacy and Safety



Efficacy

- Decrease in IOP for nonselective agents ranges from 20% to 30%[a-e]
  - Long-term use of timolol reported to reach a 35% reduction
- Betaxolol reduces IOP by 23% at trough and 26% at peak[a]

Safety

- Stinging, burning, red eye, itching, tearing, and loss of corneal sensitivity most common[f]
- Bronchospasm and reduced heart rate are possible[a,g]
  - More common in patients treated with nonselective agents vs betaxolol
  - Avoid use in patients with underlying cardiovascular or pulmonary conditions such as asthma[a]

a. Sambhara D, et al. Ther Adv Chronic Dis. 2014;5:30-43; b. Negri L, et al. J Ophthalmol. 2019;2019:4146124; c. Rakofsky SI, et al. Can J Ophthalmol. 1989;24:2-6; d. Tara G, et al. Metipranolol. In: xPharm: The Comprehensive Pharmacology Reference. Elsevier;20071-4; e. Stewart WC, et al. Am J Ophthalmol. 1997;124:498-505; f. Zimmerman TJ. J Ocul Pharmacol. 1993;9:373-384.

37

Selective Alpha-2 Agonists

Most frequently used are brimonidine and apraclonidine

Alpha-2 agonists stimulate vascular post-junctional alpha-2 receptors

- Decreases intracellular cAMP and causes ciliary body and episcleral vasoconstriction, reducing the production of aqueous humor and increasing outflow

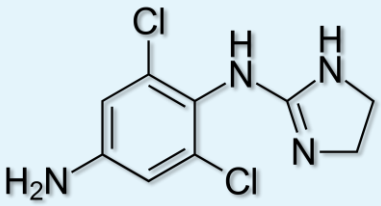
Apraclonidine is instilled 2 to 3 times daily and brimonidine up to twice daily

Brimonidine is a category B medication and can be considered for pregnant patients

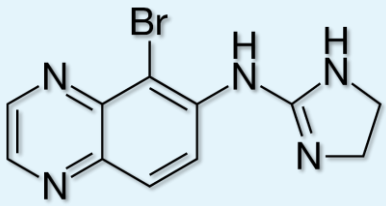
38

Alpha-2 Agonists: Efficacy and Safety

Apraclonidine



Brimonidine



Apraclonidine

- Decreases IOP ~20%
- Common ocular AEs include conjunctival hyperemia, itching and foreign body sensation, and tearing
- Common nonocular AEs include dry mouth and unusual taste perception
- High rates of tachyphylaxis and potential for systemic hypotensive effects limit use

Brimonidine

- Decreases IOP ~20-27%
  - Peak effects occur 2 hours after instillation, with a trough 12 hours after instillation
- Most significant local adverse reaction is allergic blepharoconjunctivitis
- Most common systemic effects include dry mouth and dry nose

39

Topical Carbonic Anhydrase Inhibitors (CAIs)

Used for many decades to treat glaucoma

Topical CAIs include dorzolamide and brinzolamide

Suppress production of aqueous humor at the ciliary body by decreasing the production of bicarbonate ions[a]

- Thought to influence fluid transport by a pH-dependent sodium transport

Are good adjunctive agents

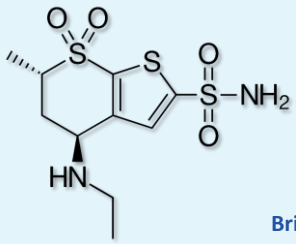
- Work synergistically with other classes of topical antiglaucoma agents
- Potential for 24-hour IOP lowering

Administered 3 times daily as monotherapy and 2 times daily as a combination therapy

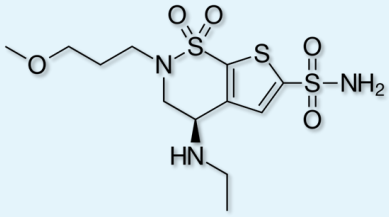
40

Dorzolamide and Brinzolamide

Dorzolamide



Brinzolamide



Efficacy[a]

- Associated with IOP reductions of ~20%
  - Peak effect occurs at 2 hours after instillation with trough at 8 hours

Safety[a,b]

- Most common ocular AEs include stinging, burning, and itching
- Blepharoconjunctivitis and altered corneal endothelial function are rare
- Brinzolamide is associated with less ocular surface discomfort
- Systemic AEs are a possibility, though rare
  - 1 case of topical CAI-induced thrombocytopenia was reported with dorzolamide 2%

a. Dikopf MS, et al. Expert Opin Pharmacother. 2017;18:885-898; b. Ringeisen AL, et al. EyeWiki. Updated March 21, 2023. Accessed May 15, 2023.

41

Fluid Reducers - A Discussion

When do you consider a beta blocker vs a selective alpha-2 agonist or carbonic anhydrase inhibitor?

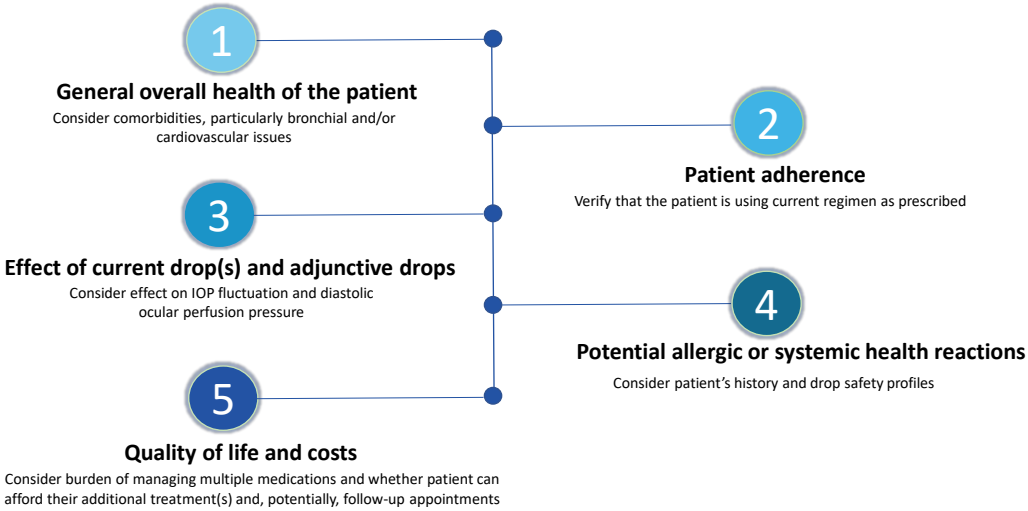
Do you consider a drop's mechanism of action (ie, whether it helps drain aqueous humor vs reduce its production)?

42

Combining Agents and Using Combination Drops

43

Considerations When Adding Another Drop



Asrani S. Rev Ophthalmol. Published 2016. Accessed May 15, 2023.

44

Fixed-Dose Combination Eye Drops: Benefits

Nearly 75% of patients with glaucoma are treated with > 1 medication for long periods of time, often years[a]

- Offer the convenience of using 1 eye drop bottle instead of 2, potentially improving adherence and reducing medication dosing errors[a,b]
- Exhibit a comparable or improved safety and tolerability profile vs use of their constituents, and may reduce exposure to preservatives[b]
- Offer possible financial advantage, depending on prescribed treatment and patients' insurance plan[c]

a. AAO and AGS. Statement on Glaucoma Eye Drops. Published 2014. Accessed May 15, 2023; b. Konstas AG, et al. Expert Opin Drug Saf. 2020;19:1445-1460; c. Glaucoma Research Foundation. Guide to Glaucoma Medications. Reviewed March 17, 2023. Accessed May 15, 2023.

45

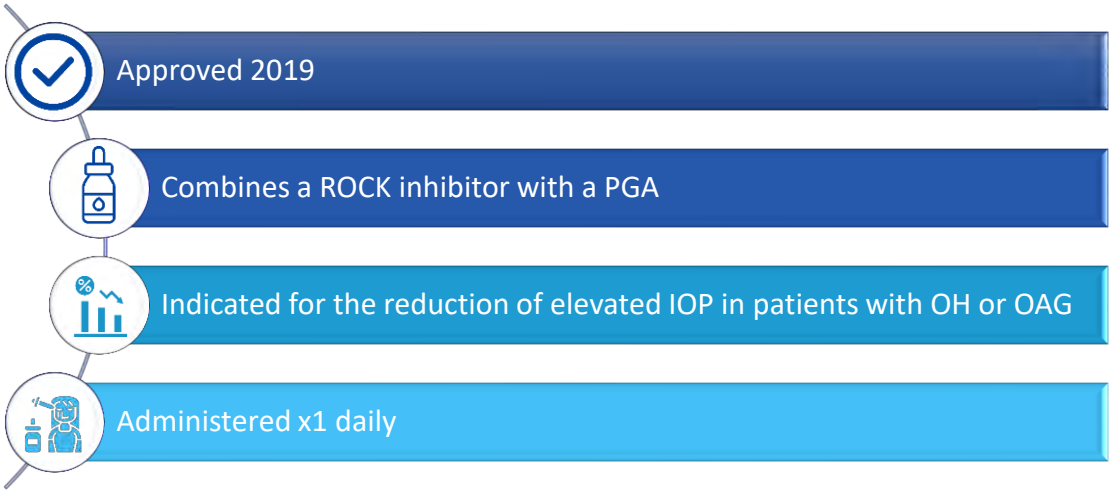
Older FDA-Approved Fixed-Dose Combinations

Combination	Overview
Timolol 0.5%-dorzolamide 2%[a,b]	• Approved 1998 • Preservative-free option available • Combines a beta blocker with a CAI • Indicated for patients insufficiently responsive to beta-blockers • Administered x2 daily
Timolol 0.5%-brimonidine 0.2%[c]	• Approved 2007 • Preservative-free option available • Combines a beta blocker with a CAI • Indicated for patients who require adjunctive/replacement therapy due to inadequately controlled IOP • Administered x2 daily
Brinzolamide 1%-brimonidine 0.2%[d]	• Approved 2013 • Combines a CAI with an alpha-2 adrenergic receptor agonist • Indicated for the reduction of elevated IOP in patients with OH or OAG • Administered x3 daily

a. Konstas AG, et al. Expert Opin Drug Saf. 2020;19:1445-1460; b. Dorzolamide hydrochloride-timolol maleate ophthalmic solution [prescribing information]. Approved April 1998; c. Brimonidine tartrate/timolol maleate ophthalmic solution [prescribing information]. Approved 2007. Updated October 2015; d. Brinzolamide/brimonidine tartrate ophthalmic suspension [prescribing information]. Approved 2013. Updated April 2013.

46

Netarsudil 0.02%-Latanoprost 0.005%



Netarsudil and latanoprost ophthalmic solution [prescribing information]. Approved 2019. Updated June 2020.

47

Netarsudil-Latanoprost: Efficacy and Safety

- Efficacy and safety established in MERCURY-1 and MERCURY-2 phase 3 RCTs, which compared the fixed-dose combination with its individual active components[a,b]

MERCURY-1[a]	MERCURY-2[b]
Efficacy: Netarsudil-latanoprost combination maintained statistically superior IOP lowering vs its individual components at every assessment over 12 months • Month 12: **16.2 ± 0.23 mm Hg** for netarsudil-latanoprost FDC, **17.9 ± 0.20 mm Hg** for netarsudil, and **17.6 ± 0.18 mm Hg** for latanoprost **Safety:** Combination was consistent with its individual components, with most common AE being **conjunctival hyperemia** (63% combo, 51% netarsudil, 22% latanoprost)	**Efficacy:** Netarsudil-latanoprost combination maintained statistically and clinically superior IOP lowering vs its individual components at all 9 assessments over **3 months** • Combination lowered IOP by an **additional 2.2 to 3.3 mm Hg** vs netarsudil and an additional **1.5 to 2.4 mm Hg** vs latanoprost **Safety:** No serious AEs in any arm, with minimal systemic effects; most frequent ocular AE was **conjunctival hyperemia** (55% combo, 43% netarsudil, 22% latanoprost), with most cases being mild

a. Brubaker JW, et al. Ophthalmol Glaucoma. 2020;3:327-338; b. Walters TR, et al. Ophthalmol Glaucoma. 2019;2:280-289.

48

Addressing Adherence Challenges

49

Patient Adherence Remains a Challenge

When eye drops are administered correctly, regularly, and persistently, adequate control of IOP is achievable in most patients

Adherence to treatments for glaucoma is lower than to treatments for other chronic conditions

Nonadherence typically result from a complex series of factors

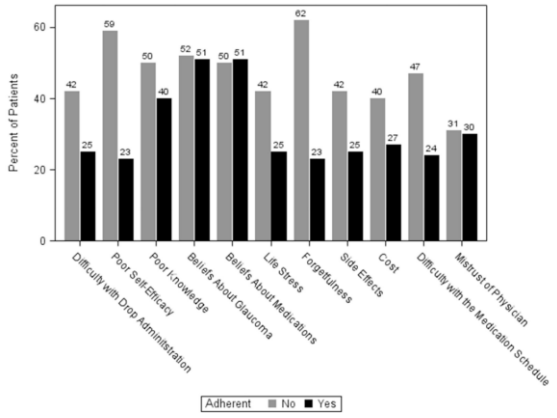
Categories into which factors contributing to nonadherence typically fall

Tapply I, et al. Patient Prefer Adher. 2021;15:1477-1489.

50

Common Self-Reported Barriers

- In a survey of adherent and nonadherent patients with glaucoma about barriers to taking their prescribed medications, 61% reported multiple barriers to treatment adherence
- The most common self-reported barriers included:
  1. Forgetfulness
  2. Poor self-efficacy
  3. Skepticism that their glaucoma would lead to vision loss
  4. Skepticism that their glaucoma medication would prevent vision loss
  5. Insufficient knowledge about glaucoma



Newman-Casey PA, et al. Ophthalmology. 2015;122:1308-1316.

51

White-Coat Adherence

Potential for white coat adherence in patients with glaucoma should not be overlooked

Describes patients' tendency to improve their adherence in the days surrounding clinic visits[a,b]

- Adherence typically rises sharply in the week leading up to their appointment

White-coat adherence can make it difficult to assess IOP control over the longer term[a,b]

Misleading IOP readings within the target range may also preclude recommendations for indicated adjunctive therapy or surgical intervention[b]

a. Schwartz GF, et al. Surv Ophthalmol. 2008;53(suppl1):S57-68; b. Poleon S, et al. Front Med (Lausanne). 2022;9:867884.

52

Administration Challenges

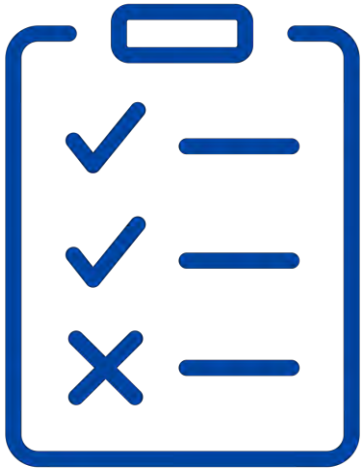
53% to 61% of patients administer > 1 drop at a time[a]

- Typically done inadvertently

One study found that patients may not administer their drops correctly or face a variety of administration challenges[b]

- 85.5% of patients were not aware of eye drops having a limited shelf-life upon opening
- 20% did not shake their ophthalmic suspensions before use
- 18.3% reported difficulty getting a drop in their eye
- 14.6% reported too many drops coming out of the bottle
- 12.2% reported difficulty squeezing the bottle

Despite such challenges, only a minority of these patients (22.7%) ever reported these problems to their clinician[b]



a. AAO and AGS. Published 2014. Accessed May 15, 2023. https://bit.ly/3oaSV4N; b. Mehuys et al. Eye. 2020;34:1392-1398.

53

Overcoming Adherence Barriers

1

Reminders

Patients can be reminded daily via text messaging, telephone, or email

2

Smart Drop Bottles and Instillation Aids

Smart drop bottles automate reminders and record delivered doses, whereas instillation aids can help patients appropriately administer eye drops in the absence of a caregiver

3

Communication and Education

Essential for overcoming patient skepticism about the severity of glaucoma and/or the importance of medication, while also improving the likelihood that patients will administer their medications correctly

4

Preservative-Free Drops

Ideal for patients who experience uncomfortable AEs from preservative-containing topical medications

5

Changing Topical Medication Delivery Mechanisms

Switching to a treatment option that is available as single dose units, gel, or spray formulations may help, depending on identified patient challenges

Tapply I, et al. Patient Prefer Adher. 2021;15:1477-1489.

54

Concluding Remarks

- Prescription eye drops are the most common treatment for glaucoma, particularly in the frontline, but are not curative and will require daily administration
- Eye drops work via 2 key mechanisms: facilitating drainage of ocular fluid or lowering the amount of fluid produced
- PGAs continue to be a preferred first-line treatment, but beta-blockers and other agents are needed indeed.
- Most patients will eventually require multiple drops to control their IOP levels, and in this setting, fixed-dose combinations may be a good option for some patients
- Regardless of the drop prescribed, proper administration and treatment adherence are essential to optimize control of IOP, but there may be barriers
- Many strategies and solutions are available that can help overcome barriers, so clinicians should be vigilant about determining whether their patients are experiencing any challenges and work with them to ensure success in the administration of glaucoma medications

55

- Pinakin Davey pdavey@westernu.edu
- 909-469-8473

56