

Glaucoma Medical Management



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Disclosure

- Sanofi Speaker
- EyePromise Employee

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"All relevant financial relationships have been mitigated"

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Setting Intraocular Pressure (IOP) Target Ranges

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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			

Arsani S. [Eye Ophthalmol](#). Published 2016. Accessed May 15, 2023.

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Examining Eye Drops for Glaucoma

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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://dall-e.openai.com/>

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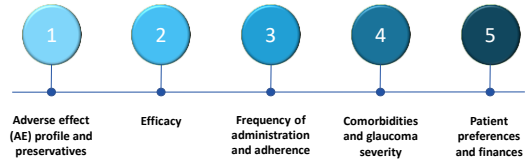
FDA-Approved Eye Drops

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

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>

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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 AOS. *Statement on Glaucoma Eye Drop Availability*. Published 2014. Accessed May 15, 2023.

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Prostaglandin Analogues (PGAs)

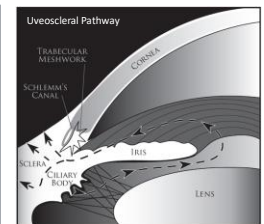
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PGAs and Uveoscleral Outflow

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



Intaglietta F, et al. *J Pharmacol*. 2010;576:1079-1089.
Image by Goff M, et al. *The Open Ophthalmology Journal*. 2010;4:52-59.

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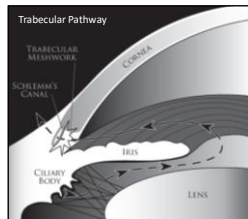
PGAs and Trabecular Outflow

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

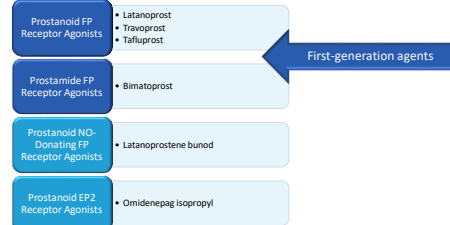
- Loss of extracellular matrix from the juxtacanalicular region and cell disconnection from the extracellular matrix
- EP receptor stimulation, alters cell contractility of the trabecular meshwork
- Altered production of MMPs



EP, E-prostanoid; MMPs, matrix metalloproteinases.
Winkler NS, et al. *J Ocul Pharmacol Ther*. 2014;30:103-109.
Image by Goff M, et al. *The Open Ophthalmology Journal*. 2010;4:52-59.

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FDA-Approved PGAs



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PGAs: Benefits and Issues

Benefits

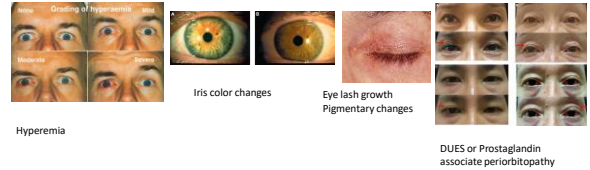
- Highly effective
- Once-daily dosing makes them an ideal choice for monotherapy
- Limited AE profile
 - Most common AEs are conjunctival hyperemia and inflammation
 - No systemic effects

Issues

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

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F2 alpha Prostaglandin related side effects



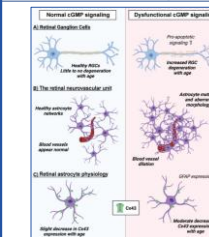
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A Discussion of first generation PGA agents

When, How and Why?

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NO-Donating FP Receptor Agonists: Overview

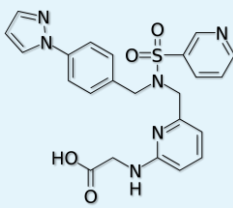


- NO and its second messenger cGMP are important in IOP regulation^[a,b]
- NO-donating PGAs lower IOP via unconventional and conventional pathways^[c]
 - Enhanced uveoscleral outflow via FP receptor activation
 - Greater trabecular meshwork outflow via cGMP stimulation
- Latanoprostene bunod 0.024% (LBN)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

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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^[c]

a. Koury C. *Ophthalmology*. 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.

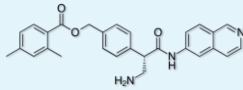
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Other Drops Draining Excess Aqueous Humor

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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^[c]

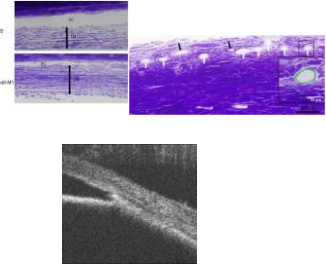
- Instilled in the evening

NET, norepinephrine transporter; OAG, open-angle glaucoma; ROCK, rho kinase.
a. Patel P et al. [JAMA Ophthalmol](#). 2017;35(11):1251-1252. b. [Glaucoma Today](#). Published September/October 2017. Accessed May 15, 2023.
c. [Glaucoma Today](#). Published September/October 2017. Accessed May 15, 2023.

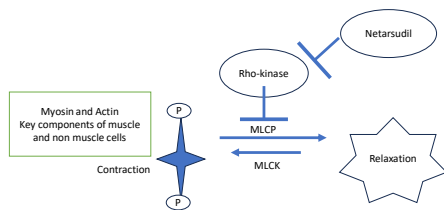
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Netarsudil (AERI pharma) Rhopressa™

- Another class of ROCK-inhibitor Small-molecule
- Alter TM cells
- Alters norepinephrine transporter (NET)-
 - NET inhibitor to lower aqueous production
- Changes episcleral venous pressure



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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^[d]

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;360:927-948. c. Fridman G, et al. *J Ocul Pharmacol Ther*. 2022;37:338-342.

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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)

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Eye Drops That Reduce Fluid Production

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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]

Second most often used class of medication for glaucoma

- 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

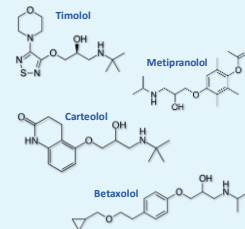
Can be administered once or twice daily^[c]

- Aqueous solutions and gel formulations are available

a. Karmel M, et al. [Evident 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.

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Beta Blockers: Efficacy and Safety



Efficacy

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

Safety

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

a. Sambhara D, et al. *Ther Adv Chronic Dis*. 2014;5:30-43. b. Negri L, et al. *J Ophthalmol*. 2019;2019:4146124. c. Rakulay S, et al. *Can J Ophthalmol*. 1989;24:2-6. d. Tera G, et al. *Metipranolol*. In: *Pharm: The Comprehensive Pharmacology Reference*. Elsevier;2007:4. e. Stewart WC, et al. *Am J Ophthalmol*. 1997;124:488-505. f. Zimmerman TJ. *J Ocul Pharmacol*. 1993;9:379-384.

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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 also BID or TID

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

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Alpha-2 Agonists: Efficacy and Safety



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

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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

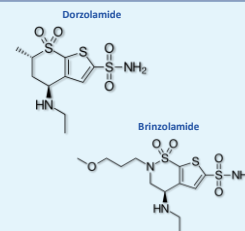
Are good adjunctive agents

- 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

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Dorzolamide and 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%

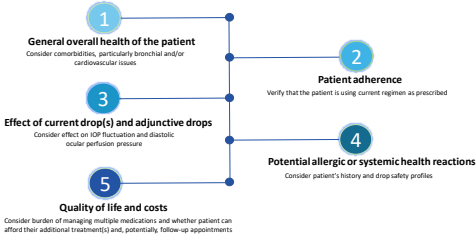
a. Dileep MS, et al. *Expert Opin Pharmacother*. 2017;18:885-896. b. Ringstein AL, et al. [Evident](#). Updated March 21, 2023. Accessed May 15, 2023.

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Combining Agents and Using Combination Drops

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Considerations When Adding Another Drop



Arani S. [Eye Ophthalmol](#). Published 2018. Accessed May 15, 2023.

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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.

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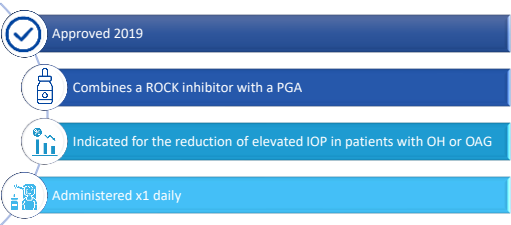
Older FDA-Approved Fixed-Dose Combinations

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 2023.

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Netarsudil 0.02%-Latanoprost 0.005%



Netarsudil and latanoprost ophthalmic solution [\[prescribing information\]](#). Approved 2019. Updated June 2020.

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Addressing Adherence Challenges

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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

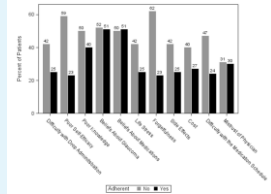


Tapilly I, et al. Patient Prefer Adher. 2021;15:1477-1489.

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Common Self-Reported Barriers

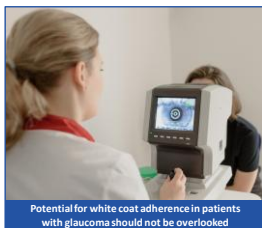
- In a survey of adherent and nonadherent patients with glaucoma about barriers to taking their prescribed medications, 61% reported multiple barriers to treatment adherence
- The most common self-reported barriers included:
 1. Forgetfulness
 2. Poor self-efficacy
 3. Skepticism that their glaucoma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



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

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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^[a]

a. Schwartz GF, et al. Surv Ophthalmol. 2008;53(suppl1):57-68; b. Poleon S, et al. Front Med (Lausanne). 2022;9:867884.

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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

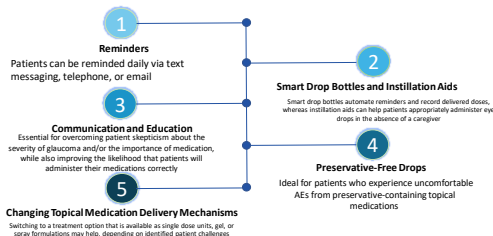
Despite such challenges, only a minority of these patients (22.7%) ever reported these problems to their clinician^[b]



a. AAO and AGS. Published 2014. Accessed May 15, 2023. <https://bit.ly/3ooV4b5>; b. Muthyry et al. Eye. 2020;34:1392-1398.

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Overcoming Adherence Barriers



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

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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

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