

IOP-lowering therapy: current treatment options and future opportunities

Glaucoma Education Working Group

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Abstract

- Intraocular pressure (IOP) homeostasis in normal eyes is maintained by a balance between aqueous humor production and outflow; most outflow is through the conventional pathway via the trabecular meshwork (TM)
- Today's commonly prescribed classes of IOP-lowering drugs work primarily by decreasing aqueous humor production or increasing outflow through the unconventional (uveoscleral) pathway
- Although TM dysfunction leading to decreased trabecular outflow is thought to be the cause of elevated IOP in glaucoma, none of the commonly used agents work primarily by targeting the TM
- Unmet needs with current IOP-lowering therapies exist in the areas of efficacy, safety, and dosing complexity, providing multiple opportunities for improvement with future treatments
- In particular, agents that act by restoring outflow through the TM could provide multiple potential benefits and complement the actions of each of the current classes of IOP-lowering therapies

The science of IOP homeostasis—the key to understanding current IOP-lowering treatments

IOP homeostasis in normal eyes is maintained by a balance between 2 main dynamics—the rate of production of aqueous humor in the eye, and the rate at which it flows out through various pathways (Figure 1).^{1,2}

- Aqueous humor is primarily produced via active secretion by the ciliary body into the posterior chamber¹⁻³
- Aqueous humor flows from the posterior chamber through the pupil into the anterior chamber and exits the eye through passive flow via 2 pathways¹⁻³
 - Through the TM into Schlemm's canal and subsequently into the episcleral veins via collector channels—the **trabecular, or conventional outflow pathway**
 - Through the peripheral base of the iris, into the ciliary body, and through the sclera—the **uveoscleral, or unconventional outflow pathway**

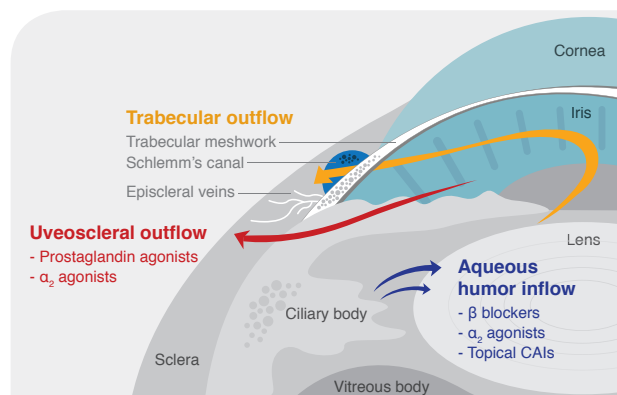


Fig 1: Schematic of anterior portion of the eye highlighting anatomy relevant to IOP homeostasis and indicating the specific aspects affected by current, commonly used classes of IOP-lowering therapies.³

In normal eyes, outflow is roughly equal between the trabecular and uveoscleral pathways, but only about 20% happens through the uveoscleral pathway in glaucomatous eyes.^{4,5} The TM accounts for about half of the resistance to outflow in normal eyes, but up to about 70% in glaucomatous eyes. The remaining resistance is beyond Schlemm's canal⁶; episcleral venous pressure (EVP), estimated to be 6-11 mm Hg in various studies, also contributes significantly to IOP.^{7,8}



Pathways of IOP homeostasis and current IOP-lowering therapies

Although the 4 most commonly prescribed classes of IOP-lowering agents act on diverse molecular targets, most of them ultimately affect the same pathway within IOP homeostasis. Three of the 4 most commonly used classes reduce IOP primarily by **decreasing aqueous humor inflow** (Figure 2)²⁻⁴:

- β blockers (eg, timolol), the gold-standard therapy in decades past
- α_2 agonists (eg, brimonidine)
- Topical carbonic anhydrase inhibitors (CAIs) (eg, dorzolamide, brinzolamide)

Prostaglandin agonists (PGAs) (eg, latanoprost) are the only agents that mainly affect outflow. As current first-line therapies of choice, **PGAs primarily reduce IOP by increasing uveoscleral outflow**²⁻⁴ (although secondary effects on TM outflow may occur with bimatoprost⁴). Certain α_2 agonists are also thought to have effects on uveoscleral outflow as a secondary mechanism of action.²⁻⁴

Fig 2: Commonly used classes of IOP-lowering agents, their proposed mechanisms of action, and the year they were approved by the FDA.²⁻⁴

Class of IOP-Lowering Agents	Mechanism of Action	Year Introduced
β blockers	Decrease aqueous humor inflow	1978 (timolol maleate)
α_2 agonists	Decrease aqueous humor inflow; brimonidine also increases uveoscleral outflow	1988 (apraclonidine) 1996 (brimonidine tartrate)
Topical CAIs	Decrease aqueous humor inflow	1995 (dorzolamide) 1998 (brinzolamide)
PGAs	Primary: increase uveoscleral outflow Secondary (potentially with bimatoprost): increase trabecular outflow ⁴	1996 (latanoprost)

No agents commonly used today reduce IOP primarily by increasing trabecular outflow³⁻⁴

In glaucomatous eyes, the cause of elevated IOP is a decrease in trabecular outflow facility due to degenerative anatomical changes in the TM. This has been confirmed by studies showing a correlation between changes in the TM and reduction in trabecular outflow, leading to elevated IOP in glaucoma. The changes include endothelial cell loss, fusion of adjacent trabecular beams due to beam widening and deposition of plaque material, and alterations in TM tissue stiffness and contractility associated with over-production and deposition of extracellular matrix in the TM (Figure 3)^{1,9-12}.

Since the TM is avascular, it relies on the flow of aqueous humor to supply the nutrients, growth factors, and antioxidants it needs. Anything that limits the flow of aqueous humor through the TM could promote further anatomical changes.¹⁰

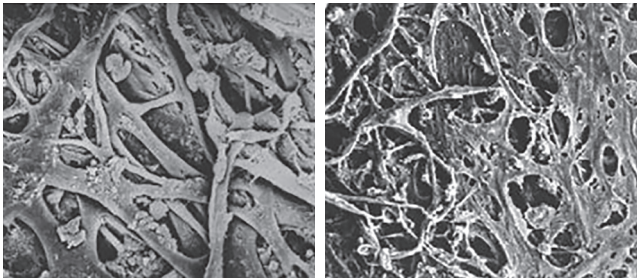


Fig 3: Alterations in the TM detected using scanning electron microscopy (x2000) under physiological conditions (left) and in primary open angle glaucoma (POAG) (right).¹¹



Areas of remaining unmet need in IOP-lowering therapy

Despite the impressive advances that have been made in IOP-lowering therapy since 1978 when timolol maleate first became available in the US, there are still areas in which treatment remains less than optimal.²

Efficacy gaps persist

- While improved efficacy, tolerability, and once-daily dosing have made PGA monotherapy the mainstay of first-line IOP-lowering therapy, **40-75% of patients fail to achieve sufficient IOP reduction with monotherapy after more than 2 years**^{2,13}
 - As a result, most patients require ≥ 2 medications to reach IOP goal²
- Among agents used adjunctively or in later-line therapy, timolol still provides the greatest IOP reduction—**other options have been unable to demonstrate non-inferiority to timolol** in patient registration studies^{2,14,15}
- Providing consistent IOP control that minimizes 24-hour IOP fluctuation remains challenging—**timolol, brimonidine, and even latanoprost have been shown to provide less IOP reduction during the nighttime** compared with daytime⁴
- Over long-term treatment, **diminishment of early IOP reduction has been seen in up to 40% of patients treated with timolol or latanoprost**¹⁶
 - Both diurnal and long-term IOP fluctuation are correlated with increased risk of glaucomatous damage^{17,18}

Patients achieving insufficient IOP reduction on monotherapy	40-75%
Adjunctive IOP-lowering agents showing non-inferiority to timolol for IOP reduction	0
Agents showing less IOP reduction during nighttime vs daytime	Timolol, brimonidine, latanoprost
Loss of early IOP reduction over long term with timolol or latanoprost	Up to 40% of patients

Complexity and safety issues create barriers

Given that many patients will need 2 or more drugs to achieve their IOP goal, the practical burdens of daily topical treatment can be substantial.

- Since only the PGAs are used once daily, **combination treatment with adjunctive agents introduces the complexity of mixed dosing schedules**²
 - Patients may need to keep track of administering different drops once, twice, and 3 times per day, depending on the regimen²
 - Fixed-dose combinations (FDCs) may help some patients, but since currently available FDCs in the US are dosed 2-3 times daily, adding a FDC to a PGA still requires adherence to a mixed dosing schedule¹³

Adherence to topical IOP-lowering therapies remains a challenge, even with a single, once-daily agent. The increasing complexity and burden of treatment with multiagent regimens may exacerbate the problem.^{13,19}

Current adjunctive agents can also introduce safety issues that may adversely affect patients.

- Topical administration of some IOP-lowering drops can lead to substantial systemic exposure and **potential for attendant systemic side effects**² (Figure 4)

Fig 4: Classes of IOP-lowering agents and common side effects.²

Class of IOP-Lowering Agents	Common Systemic Side Effects
β blockers	Bronchospasm, bradycardia, hypotension (especially nocturnal)
α_2 agonists	Headache, palpitations, anxiety, hypertension, fatigue



Challenges for future exploration in IOP-lowering therapy

For those engaged in the search for the next generation of IOP-lowering therapies, the challenges described above can help identify areas of research in which meaningful opportunities may be found.

Reviewing the pharmacology of the current topical therapies for IOP reduction puts a spotlight on one obvious opportunity—the **unfilled position in the treatment armamentarium for an agent that reduces IOP primarily by increasing trabecular outflow**. Given the importance of degeneration of the TM in glaucoma, the challenge of filling this position takes on even greater urgency.^{1,3,9} With a unique mechanism of action among the available treatments, an agent acting on the TM would theoretically act as a complement to any of the currently available classes of agents, including the FDCs, and could help increase the supply of nutrients, growth factors, and antioxidants needed to maintain a healthy TM.¹⁰

The gaps in efficacy described above also indicate other potentially productive areas for exploration. In particular, finding **an adjunctive therapy that can show IOP reduction that is non-inferior to timolol**, but without the systemic safety concerns, would be a worthy goal. Likewise, an agent that can provide **consistent diurnal IOP reduction and sustained long-term IOP control** would be a welcome advance.

Of course, clinicians know that no matter how effective a therapy may be, it can only work if the patient is able to take it accurately and consistently, without interruption over time. The complex dosing and potential systemic safety concerns with some of today's treatments leave a wide-open door for new solutions that can **reduce the burden of therapy and facilitate the IOP control** that patients need to preserve their vision.



While not simple to solve, these challenges present opportunities to do even more for our patients who need IOP control.

References: 1. Goel M, Picciani RG, Lee RK, Bhattacharya SK. *Open Ophthalmol J*. 2010;4:52-59. 2. Crawley L, Zamir SM, Cordeiro MF, Guo L. *Ophthalmol Eye Dis*. 2012;4:43-64. 3. McLaren NC, Moroi SE. *Pharmacogenomics J*. 2003;3:197-201. 4. Malihi M, Sit AJ. *Int Ophthalmol Clin*. 2011;51(3):119-139. 5. Toris CB, Yablonski ME, Wang YL, Camras CB. *Am J Ophthalmol*. 1999;127(4):407-412. 6. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. *Curr Eye Res*. 1989;8(12):1233-1240. 7. Sit AJ, McLaren JW. *Exp Eye Res*. 2011;93(3):291-298. 8. Sit AJ, Ekdawi NS, Malihi M, McLaren JW. *Exp Eye Res*. 2011;92(6):537-544. 9. Schmidl D, Schmetterer L, Garhöfer G, Popa-Cherecheanu A. *J Ocul Pharmacol Ther*. 2015;31(2):63-77. 10. Kopczyński CC, Epstein DL. *J Ocul Pharmacol Ther*. 2014;30(2-3):85-87. 11. Sacca SC, Pulliero A. *J Cell Physiol*. 2015;230:510-525. 12. Sihota R, Goyal A, Kaur J, Gupta V, Nag TC. *Indian J Ophthalmol*. 2012;60(3):183-188. 13. Fechtner RD, Khouri AS. *Glaucoma Today*. 2016 November/December:33-36. 14. Center for Drug Evaluation and Research. Medical Officer's Review of NDA 20-816, Part 2. http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20816_AZOPT_MEDR_P2.PDF. August 5, 1997. Accessed September 25, 2016. 15. Schuman JS. *Surv Ophthalmol*. 1996;1:S27-S37. 16. Hedman K, Alm A. *Eur J Ophthalmol*. 2000;10(2):95-104. 17. Asrani S, Zeimer R, Wilensky J, et al. *J Glaucoma*. 2000;9(2):134-142. 18. The AGIS Investigators. *Am J Ophthalmol*. 2000;130(4):429-440. 19. Reardon G, Schwartz GF, Mozaffari E. *Am J Ophthalmol*. 2004;137(suppl 1):S3-S12.

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The journey to innovation continues