


CME MONOGRAPH



THE PRESSURE IS *STILL ON!* Current and Emerging Therapies for Managing Glaucoma

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Glaucoma continues to be the leading cause of irreversible blindness worldwide. New methods of assessing patient risk have been identified, and new therapies for decreasing intraocular pressure (IOP) have been developed. One new therapeutic mechanism for glaucoma involves the role of nitric oxide on IOP regulation. In addition, alternative drug delivery methods have been invented. The purpose of this activity is to update ophthalmologists on the mechanisms of action of current and emerging glaucoma therapies and to assess traditional and emerging risk factors for disease progression.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists caring for patients with glaucoma.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Outline the relationship between the sites of action and selection of IOP-lowering therapies
- Discuss the role of nitric oxide in IOP regulation
- Describe the mechanism of action of current and emerging topical glaucoma therapies
- Evaluate the clinical relevance of safety and efficacy data for emerging topical therapies for the treatment of glaucoma
- Assess traditional and emerging risk factors for progression in patients with ocular hypertension or glaucoma

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THE PRESSURE IS STILL ON!

Current and Emerging Therapies for Managing Glaucoma

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness that affects millions of people worldwide.¹ New risk factors and new therapies for glaucoma have emerged. Low ocular perfusion pressure (OPP) and low cerebral spinal fluid pressure (CSF-P) may be indicators of disease progression. Current therapies aim to lower intraocular pressure (IOP) by aqueous suppression or by increasing uveoscleral outflow. Furthermore, pilocarpine, which works indirectly on the trabecular meshwork (TM) via ciliary body contraction, is still used in some patients. There are no available therapies targeting outflow through direct action on the TM, a major contributor to aqueous outflow in normal eyes. Emerging therapies, such as latanoprostene bunod (LBN) and netarsudil, may change the treatment landscape of this disease by lowering IOP in patients with glaucoma through this mechanism. Herein, the current state of glaucoma management is described.

DEFINING GLAUCOMA: AN UPDATE FROM THE AMERICAN ACADEMY OF OPHTHALMOLOGY

In the September 2015 Preferred Practice Pattern updates, the American Academy of Ophthalmology defined primary open-angle glaucoma (POAG) as "...a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy."²

RISK FACTORS OF GLAUCOMA

The American Academy of Ophthalmology Glaucoma Preferred Practice Pattern guidelines recognize several risk factors that have been identified in carefully conducted population-based studies. Intraocular pressure, age, race, and family history are long-standing glaucoma risk factors. The potential role of IOP has long been recognized as important in the pathophysiology of glaucoma. Furthermore, lowering IOP has been found to decrease the risk of optic nerve damage and blindness. Older age is also a known risk factor for the development of POAG; it has been estimated that 31% of patients with POAG in the United States are aged 70 to 79 years.³ Prevalence of glaucoma in the siblings of patients is 10.4%, and 1.1% in the offspring of patients.⁴ Overall, first-degree relatives of patients with glaucoma have a 9.2-fold higher relative risk of developing glaucoma.⁴ With regard to race, African Americans and Latinos are at a higher risk of developing glaucoma than are whites.^{5,6} The rising Hispanic population in the United States is expected to make up the largest group of patients with this disease by 2035.³

Particular structural and functional abnormalities in the eye may also be a risk factor. Measuring central corneal thickness is an important component of a complete ocular examination.⁷

A measurement of $< 555 \mu\text{m}$ is associated with a greater risk of glaucoma development than a central corneal thickness of $\geq 588 \mu\text{m}$.² Large studies have identified an increased prevalence of POAG in patients with myopia²; this occurrence has been proposed to be caused by weaker scleral support, which may cause patients to be more susceptible to retinal and optic nerve damage.²

Emerging risk factors include low CSF-P and low OPP, both of which correlate with optic nerve damage. The optic nerve can be affected by 2 pressurized regions: the pressure of the intraocular space (ie, IOP) and the pressure from the subarachnoid space, which is caused by cerebrospinal fluid.^{8,9} The lamina cribrosa is in between these 2 opposing regions, and the pressure difference between them (translaminar pressure difference) can cause structural alterations to the optic disc.^{8,9} Similarly, the optic nerve cupping observed in patients with elevated IOP could also occur in patients with low CSF-P.^{8,9} Both a prospective and a retrospective study showed that CSF-P was significantly lower in patients with glaucoma ($P < .001$).^{8,9} In the prospective study, loss of vision was positively correlated with translaminar pressure difference and negatively correlated with CSF-P.⁸ However, performing a lumbar puncture does not necessarily represent CSF-P, and such a procedure may not be a practical part of an ophthalmological evaluation. Noninvasive methods of measuring CSF-P are under development.

The Baltimore Eye Survey, Egna-Neumarkt Study, Proyecto VER, and Barbados Eye Survey all identified low OPP as a significant risk factor for POAG.^{5,10-13} Ocular perfusion pressure represents the relative pressure at which blood perfuses the eye and is the difference between systemic blood pressure (BP) and IOP. Either low BP or high IOP can lead to low OPP and an increased risk of developing POAG.¹³ In a study that measures the relation between OPP and glaucoma, it is impossible to separate the individual effects of IOP and BP when measuring OPP unless there is simultaneous control for both IOP and BP.^{14,15}

In the Barbados Eye Study, use of a multivariable model did demonstrate an inverse relation between OPP and POAG, even after controlling for BP and IOP.¹³ On the other hand, the Rotterdam Study strongly supports that controlling for IOP resulted in a null association between OPP and incident open-angle glaucoma.¹⁶

It is possible that treatment of systemic hypertension could modify the risk of POAG. In considering this matter, one must account for the type of BP treatment (diet, drugs, and type of drugs) and the effectiveness of that treatment. In the Egna-Neumarkt Study, hypertension was adversely associated with POAG, but not with being on medication.¹¹ Conversely, the Blue Mountains Eye Study showed that untreated hypertension was not a strong risk factor for glaucoma, but that patients who had hypertension, despite being treated with antihypertensive medication, were at risk for POAG.¹⁷ Although there are studies that did not find a correlation with antihypertensive medication and POAG,^{18,19} the European Glaucoma Treatment Study showed that the diuretic dorzolamide may be a risk factor for glaucoma.²⁰

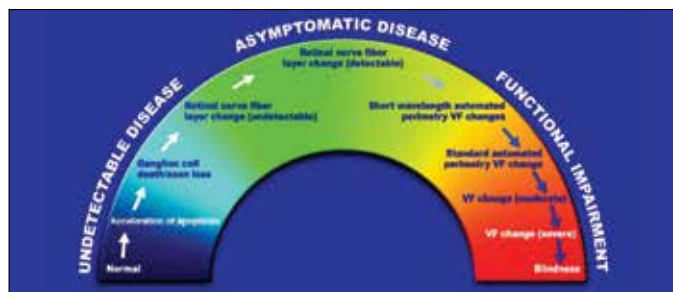


Figure 1. A spectrum of glaucoma progression illustrates early, undetectable changes through advanced disease with blindness.²¹

Reprinted from *American Journal of Ophthalmology*, 138, Weinreb RN, Friedman DS, Fechtner RD, et al. Risk assessment in the management of patients with ocular hypertension, 458-467, Copyright 2004, with permission from Elsevier.

Abbreviation: VF, visual field.

INCIDENCE OF GLAUCOMA AND DISEASE PROGRESSION

The estimated number of people with POAG and angle-closure glaucoma worldwide is expected to increase to approximately 80 million by 2020.¹ Approximately 8.4 million patients with glaucoma have bilateral blindness, and this number is expected to rise to 11.1 million by 2020.¹

The progression from asymptomatic disease to blindness is a multistep process that takes years to manifest. Weinreb and colleagues describe a “glaucoma continuum” that illustrates the ocular deterioration that occurs throughout the course of disease (**Figure 1**).²¹ Years of apoptotic retinal ganglion cell death have already taken place before any retinal damage can be detected.²¹ Factors that can cause retinal nerve damage and death include increased IOP levels, inflammatory signals, ischemia, and autoimmunity.²² It is only after the retinal nerve fiber layer deteriorates that disease begins to be detectable by visual field testing.

Visual impairment from retinal nerve fiber damage is irreversible, so although treatment is typically recommended upon detectable damage,²¹ patients with elevated IOP, thin central corneal thicknesses, and enlarged cup/disc ratios might benefit from preventative treatment.²³ Preventative treatment with IOP-reducing medication has been shown to reduce the risk of developing glaucoma, particularly in patients with $> 13\%$ estimated 5-year risk of developing POAG.²⁴

Recently, intake of nitrates from leafy green vegetables (240 mg/d) has been shown to reduce the relative risk of developing POAG with paracentral vision loss by 44%; moreover, nitrate intake reduces the relative risk of developing all forms of POAG by 21%.²⁵ In our bodies, nitrates are converted into nitrites, which can be further reduced into nitric oxide (NO), a signaling molecule that relaxes smooth muscles. Several preclinical studies have demonstrated that by relaxing the smooth muscles in ocular tissue (ie, TM), aqueous humor outflow increases, resulting in reduced IOP.²⁶

PATHOPHYSIOLOGY OF GLAUCOMA

There is still much to be elucidated regarding the pathophysiology of this disease. Glaucoma is a multifactorial disease that results in structural and functional damage to the retina and optic nerve. Aqueous humor production by the ciliary body and its drainage through uveoscleral outflow and the TM modulate IOP.²⁷ Blockage or resistance to aqueous outflow

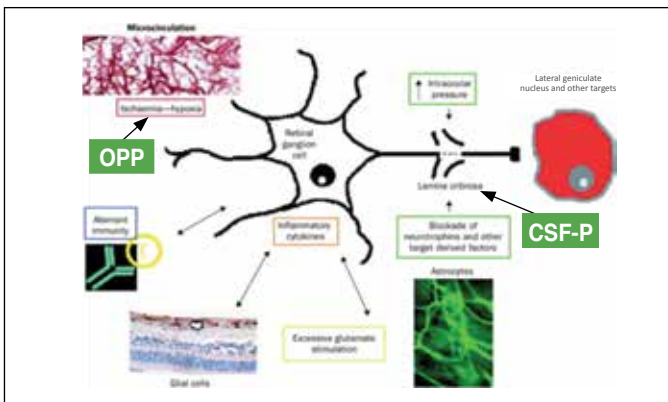


Figure 2. The pathophysiology of open-angle glaucoma is multifaceted. Risk factors, such as IOP, low OPP, and low CSF-P can affect ocular structures, resulting in retinal ganglion damage and glaucoma progression.²²

Adapted from *The Lancet*, 363, Weinreb RN, Khaw PT, Primary open-angle glaucoma, 1711-1720, Copyright 2004, with permission from Elsevier.

Abbreviations: CSF-P, cerebrospinal fluid pressure; IOP, intraocular pressure; OPP, ocular perfusion pressure.

increases IOP, leading to damage to the lamina cribrosa and, eventually, to the optic nerve fibers.²⁷

On a cellular level, many contributing mechanisms have been proposed to explain how ocular degeneration occurs in glaucoma (**Figure 2**).²² The axonal damage induced by high IOP prevents the transport of molecules that nourish the retinal nerve fibers, which further stresses posterior eye structures.²⁸ Ocular hypertension may cause microcirculation to be blocked (hypoxia/ischemia), and the increasing pressure surrounding the ocular tissue could cause the ganglion cells to be deprived of necessary nutrients to survive.²⁷ In response to the stress and pressure, surrounding cell types, such as glial cells and astrocytes, may release factors that induce apoptotic cell death.²⁹ High IOP may cause retinal ganglion damage and death by inducing an inflammatory response.²² However, some patients with normal IOP who have glaucoma have been shown to also have altered adaptive immunity, supporting the hypothesis that inflammatory damage can cause glaucoma, dependent or independent of IOP levels.³⁰

To complicate the matter, IOP has been shown to change over 24 hours, and body position during measurement also contributes to fluctuations in IOP.³¹ Twenty-four-hour monitoring showed that IOP levels are higher at night than during the day.³¹ Physicians who consider how therapeutic options control diurnal and nocturnal IOP may be better able to elect the best treatment plan for a patient.

THERAPEUTIC TARGETS FOR GLAUCOMA TREATMENT

The goals for managing POAG include lowering IOP and maintaining a target range, preventing further damage to the optic nerve and the retinal fiber layer, and stabilizing vision.² Decreasing a patient's IOP by $\geq 25\%$ can slow glaucoma progression,³² and clinicians are recommended to begin treatments that can reduce IOP by 20% to 30% from baseline.² There are multiple sites of action for lowering IOP. Decreasing aqueous production, lowering episcleral venous pressure, and increasing uveoscleral and trabecular outflow (decrease outflow resistance) are all mechanisms that can be targeted by current drug therapies or drugs that are in late-phase clinical development (**Figure 3**).

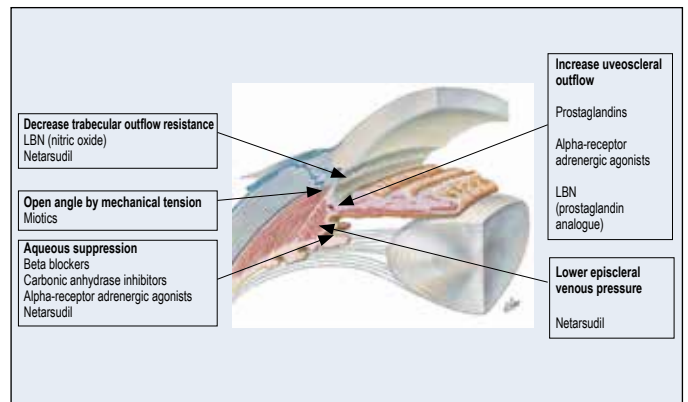


Figure 3. Glaucoma therapies and areas targeted

Note: Netarsudil and LBN are under US Food and Drug Administration review.

Abbreviation: LBN, latanoprostene bunod

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The carbonic anhydrase inhibitors (CAIs) and beta blockers lower IOP via aqueous suppression (**Figure 3**). The prostaglandin analogues (PGAs) lower IOP by increasing uveoscleral outflow, and alpha-receptor adrenergic agonists cause both aqueous suppression and increased uveoscleral outflow (**Figure 3**).

New therapies in development are the first to target outflow through the TM and other sites of action. These include NO-donating agents (PGAs and CAIs) and Rho kinase/norepinephrine transporter inhibitors.

CURRENT TREATMENTS (INTRAOCULAR PRESSURE-LOWERING MEDICATIONS)

Prostaglandin analogues are frequently prescribed as first-line therapy for POAG.² This drug class reduces IOP by increasing uveoscleral outflow of the aqueous humor.²⁷ Prostaglandin analogues are typically administered once daily at night.²⁷ To treat POAG and ocular hypertension, 3 prostaglandin analogues (latanoprost, travoprost, and bimatoprost) were US Food and Drug Administration (FDA) approved between 1996 and 2001, and they have been shown to be safe, efficacious, and relatively equivalent.^{33,34}

Beta blockers act on the beta-adrenergic receptor, which predominately lowers IOP by suppressing aqueous production in the eye.³⁵ Adverse reactions to timolol (1%-5% of patients) include itching, conjunctivitis, discharge, pain, and tearing.³⁶ Until the emergence of PGAs, timolol was the standard of care for POAG. A meta-analysis of latanoprost and timolol treatment demonstrated that although both drug classes are effective, the PGA induced a greater IOP reduction.³⁷ Currently, beta blockers are prescribed mostly as an alternative therapy to PGAs.²

The alpha-receptor adrenergic agonists and CAIs can also be prescribed, although they do not reduce IOP as effectively as do PGAs.² However, the CAI brinzolamide sustains its IOP-lowering effects at night.³⁸ Another alternative is pilocarpine, a mitotic agent that was widely prescribed before the emergence of timolol.³⁹ Pilocarpine was found to not reduce IOP as effectively as timolol, and the compound was associated with a higher incidence of adverse events.³⁹

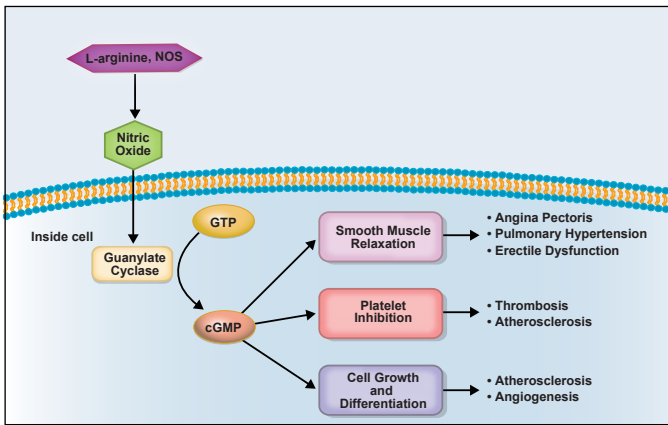


Figure 4. Nitric oxide generated in endothelial cells of blood vessels can interact with the surrounding smooth muscle cells by activating guanylate cyclase, which converts GTP to cGMP formation. When cGMP binds to the surface proteins of smooth muscle cells, relaxation is induced. In addition, cGMP can induce platelet aggregation and cell growth/proliferation.⁴²

Abbreviations: cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NOS, nitric oxide synthase.

NOVEL GLAUCOMA THERAPIES

Latanoprostene Bunod

Nitric oxide induces smooth muscle relaxation and promotes vasodilation. Nitrates such as nitroglycerin and isosorbide mononitrates have been shown to prevent cardiovascular events, such as angina, by dilating arteries.⁴⁰ A similar vasodilation mechanism as that observed in cardiovascular research occurs in the eye, and exposure to NO decreases IOP. In the eye, medications that induce production of NO have been shown to increase trabecular relaxation and allow aqueous humor outflow.²⁶ The increased outflow can decrease IOP and reduce the risk of developing glaucoma. The therapeutic benefit of NO may extend to other eye-related mechanisms because the enzymes that synthesize NO in our bodies (NO synthases [NOSs]) are present in various ocular structures. Endothelial NOS is expressed in ciliary muscle, TM, Schlemm canal, and uveal vascular endothelium, and the enzyme's role in muscle relaxation is well understood.²⁶ In addition, the expression of endothelial NOS is lower in patients with POAG.⁴¹ Neuronal NOS is found in the retina and optic nerve. Inducible NOS is expressed in the iris/ciliary body and blood vessels, particularly when inflammation aggregates, such as in individuals with increased OPP.²⁶ **Figure 4** describes the mechanism by which NO can regulate smooth muscle relaxation.⁴² Latanoprostene bunod combines latanoprost and an NO-donating moiety and was approved by the FDA on November 2, 2017.⁴³

Phase 3 APOLLO and LUNAR Trials: Latanoprostene Bunod vs Timolol

The phase 3 APOLLO and LUNAR trials were parallel studies comparing the safety and efficacy of LBN with timolol over a 3-month period.^{44,45} In both studies, 1 group of patients with POAG or ocular hypertension received LBN, 0.024%, every evening at 8 PM and placebo drops at 8 AM. The other group received timolol, 0.5%, twice daily (8 PM and 8 AM).

In the APOLLO trial, the mean baseline IOP of patients given LBN was 26.7 mm Hg and IOP was reduced by 8 to 9 mm Hg (**Table 1**).⁴⁴ The timolol treatment group had a mean baseline IOP of 26.5 mm Hg; after treatment, the mean IOP was reduced

by approximately 6.5 to 7.5 mm Hg. In total, 13% of patients receiving LBN, 0.024%, and 12% of patients receiving timolol, 0.5%, experienced adverse events. Conjunctival hyperemia occurred in 2.8% of patients receiving LBN, 0.024%, and in 1.5% of patients receiving timolol, 0.5%.

In the LUNAR trial, the mean baseline IOP was 26.5 mm Hg. This measurement was reduced by 7.5 to 8.8 mm Hg in the group receiving LBN, 0.024%, and by 6.6 to 7.9 mm Hg in the group receiving timolol, 0.5% (**Table 1**).⁴⁵ Both treatment arms experienced similar adverse events. Conjunctival hyperemia occurred in 9% of the patients receiving LBN, 0.024%, and in 0.7% of the patients receiving timolol, 0.5%.

A long-term efficacy and safety open-label 12-month extension study was conducted to further assess the results of the APOLLO and LUNAR trials.⁴⁶ After patients completed treatment from their respective trials, all were treated with LBN for an additional 9 months (APOLLO) or 3 months (LUNAR). Patients who crossed over from timolol treatment had an additional 6.3% to 8.3% decrease in diurnal IOP. The mean reduction in IOP for all patients was 32% to 34%. The most common adverse events were conjunctival hyperemia (5.9%), eye irritation (4.6%), and eye pain (3.5%).

Phase 2 VOYAGER Trial: Latanoprostene Bunod vs Latanoprost

Although phase 3 studies compared LBN to timolol, a phase 2 study on 413 patients with POAG or ocular hypertension (mean baseline IOP was approximately 26 mm Hg) was conducted to test the safety and efficacy of different doses of LBN compared with latanoprost.⁴⁷ In this study, the investigators compared the additive effect NO had on patients by comparing these 2 molecules. All 4 doses of LBN tested (0.006%, 0.012%, 0.024%, 0.040%) reduced IOP, with the efficacy plateauing at 0.024% to 0.040%. A significantly greater reduction in mean diurnal IOP was demonstrated after a 28-day treatment regimen with LBN, 0.024%, (-9.00 mm Hg) than with latanoprost, 0.005% (-7.77 mm Hg) ($P = .005$) (**Table 1**). The most common adverse events were pain at the instillation site (12% in the LBN, 0.024%, group and 6.1% in the latanoprost, 0.005%, group) and hyperemia (2.4% in the LBN, 0.024%, group and 8.5% in the latanoprost, 0.005%, group).⁴⁷

Phase 2 Constellation Trial: Latanoprostene Bunod vs Timolol Over 24 Hours

Significant reduction of nocturnal IOP with latanoprost was shown in a previous study.⁴⁸ To demonstrate that LBN has a similar effect, a crossover phase 2 study evaluated the efficacy of LBN, 0.024%, over 24-hour IOP compared with that of timolol, 0.5%.⁴⁹ The mean baseline IOP during the day in the sitting position was 21.6 mm Hg, whereas the measurement in the supine position was 24.7 mm Hg. Nocturnal mean IOP measured in the supine position was 25.7 mm Hg.⁴⁹ Both LBN and timolol reduced daytime mean IOP by 2.3 to 3.9 mm Hg ($P < .001$) in either position, but only LBN sustained a more effective control of IOP at night compared with baseline (-2.5 mm Hg) ($P = .002$) and timolol (-2.3 mm Hg) ($P = .004$).⁴⁹

RHO KINASE INHIBITORS

Rho kinases modulate structural components of various cell types, including those in the TM and Schlemm canal. Rho kinases can be inhibited directly through the use

Table 1. Clinical Trials Comparing Efficacy and Safety of LBN vs Timolol or Latanoprost^{44,45,47}

	APOLLO (Phase 3) ⁴⁴		LUNAR (Phase 3) ⁴⁵		VOYAGER (Phase 2) ⁴⁷	
Treatment	LBN, 0.024% (n = 264)	Timolol, 0.5% (n = 123)	LBN, 0.024% (n = 259)	Timolol, 0.5% (n = 128)	LBN, 0.024% (n = 83)	Latanoprost, 0.005% (n = 82)
IOP reduction, mm Hg	8-9	6.7-7.4	7.5-8.8	6.6-7.9	9	7.77
Common adverse events	LBN, 0.024% (n = 283)	Timolol, 0.5% (n = 135)	LBN, 0.024% (n = 277)	Timolol, 0.5% (n = 135)	LBN, 0.024% (n = 83)	Latanoprost, 0.005% (n = 82)
Eye irritation	3.9%	2.2%	7.2%	4.4%	3.6%	0
Conjunctival hyperemia	2.8%	1.5%	9.0%	0.7%	4.8%	0
Ocular hyperemia	NR	NR	2.5%	0.7%	2.4%	8.5%

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod; NR, not reported.

of pharmacologic inhibitors (netarsudil and ripasudil) or indirectly through NO signaling.⁵⁰ The NO–cyclic guanosine monophosphate pathway activates protein kinase G, which inhibits Rho kinase (**Figure 5**).²⁶ Inhibiting Rho kinase prevents myosin light chain phosphorylation, which prevents the interaction of actin and myosin and halts muscle contraction.²⁶ As the muscles relax, resistance in the TM decreases and aqueous humor outflow increases, which in turn lowers IOP.²⁶

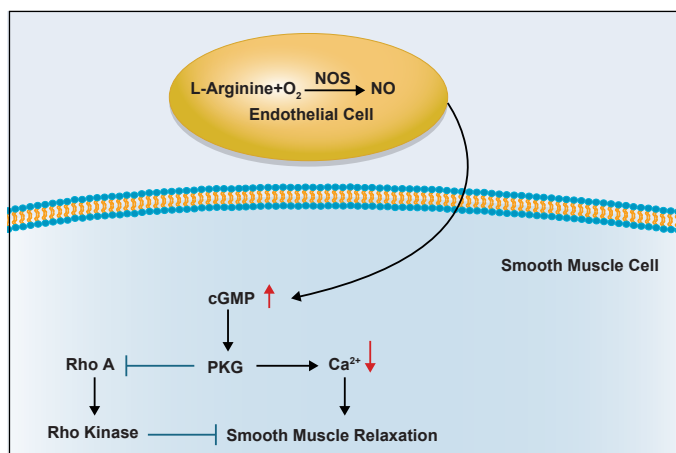


Figure 5. Nitric oxide derived from endothelial cells can diffuse into smooth muscles and induce conversion of GTP to cGMP, which activates PKG. PKG decreases intracellular calcium levels and inhibits the Rho kinase signaling pathway, resulting in smooth muscle relaxation.

Abbreviations: cGMP, cyclic guanosine monophosphate; NO, nitric oxide; NOS, nitric oxide synthase; PKG, protein kinase G.

Table 2. Clinical Trials With Netarsudil Comparing Efficacy and Safety vs Timolol^{53,54}

	Rocket 1 (Phase 3)		Rocket 2 (Phase 3)		Rocket 4 (Phase 3)	
Treatment	Netarsudil (n = 107)	Timolol (n = 120)	Netarsudil (n = 129)	Timolol (n = 142)	Netarsudil (n = 189)	Timolol (n = 199)
IOP reduction, mm Hg*	3.3-5.0	3.7-5.1	3.3-4.6	3.7-5.1	4.4-4.6	4.0-4.8
Common adverse event	Netarsudil (n = 203)	Timolol (n = 208)	Netarsudil (n = 251)	Timolol (n = 251)	Netarsudil (n = 214)	Timolol (n = 209)
Conjunctival hyperemia	53.2%	8.2%	50.2%	10.8%	42.2%	6.7%

Abbreviation: IOP, intraocular pressure.

* IOP reduction of per protocol subgroup with maximum baseline IOPs < 25 mm Hg

Netarsudil

Netarsudil (AR-13324) is an inhibitor of Rho kinase and a norepinephrine transporter. By inhibiting Rho kinase, the compound works through 3 sites of action: decreasing aqueous humor production, decreasing episcleral venous pressure, and increasing aqueous humor outflow through the TM.^{51,52} Netarsudil is currently undergoing review by the FDA. Results of recent phase 3 trials, ROCKET 1 and ROCKET 2, were reported at the 2016 Annual Meeting of The Association for Research in Vision and Ophthalmology (**Table 2**).⁵³ In each trial, netarsudil, 0.02%, was compared with timolol, 0.05%, in both untreated patients and in those previously treated with PGAs. Overall, netarsudil was noninferior to timolol in unmedicated patients with a baseline IOP < 25 mm Hg. The most common adverse event reported for a daily dose of netarsudil in ROCKET 2 was conjunctival hyperemia (50.2%). Data from the phase 3 trial, ROCKET 4, were presented at the 2017 Annual Meeting of The Association for Research in Vision and Ophthalmology (**Table 2**).⁵⁴ The baseline IOP for that study was 20.7 to 22.4 mm Hg. Netarsudil reduced IOP to 16.3 to 17.8 mm Hg, whereas timolol reduced IOP to 16.7 to 17.6 mm Hg.⁵⁴ A netarsudil/latanoprost fixed combination, 0.02%/0.005%, has been evaluated in several clinical trials. Two phase 3 trials (Mercury 1 and Mercury 2) showed that the netarsudil/latanoprost fixed combination was statistically superior to netarsudil or latanoprost monotherapy. The combination lowered IOP 1 to 3 mm Hg more than did each of its components.⁵⁵ The most common adverse event for the fixed combination was conjunctival hyperemia (53.4%).⁵⁶

Ripasudil

Ripasudil is a Rho kinase inhibitor that has been shown in clinical studies to be safe and effective. It has been approved for use in Japan since 2014.⁵⁰ As monotherapy, ripasudil lowered IOP by 2.6 to 3.7 mm Hg at 52 weeks of treatment.⁵⁷ Combination therapy with compounds such as PGAs and beta blockers resulted in additive effects.⁵⁷ There was a relatively high number (85%) of adverse drug reactions in patients. Conjunctival hyperemia (74.6%), blepharitis (20.2%), and allergic conjunctivitis (17.2%) were the most frequent adverse reactions documented.⁵⁷ The cases of conjunctival hyperemia were noted to be mostly mild (97%) and resolved on their own (78%).⁵⁷ Unlike regarding netarsudil, there are currently no plans to bring ripasudil to the United States.

Nitric Oxide–Donating Bimatoprost

Bimatoprost, a prostaglandin F_{2α} receptor analogue, lowers IOP by increasing uveoscleral outflow.⁵⁸ NCX 470 is a dual-action molecule that combines bimatoprost with an NO-donating moiety.⁵⁸ Ocular treatment with NO has been shown to relax the Schlemm canal and TM.⁵⁸ In preclinical studies, NCX 470 increased levels of cyclic guanosine monophosphate (Figure 5) in ocular tissue and is more effective at decreasing IOP than is bimatoprost at equivalent doses.⁵⁸ The first in-human phase 2 trials are expected to start early in 2018.⁵⁹

Nitric Oxide–Donating Carbonic Anhydrase Inhibitors

The CAIs dorzolamide and brinzolamide are topical drugs that lower IOP and prevent ischemic damage by inhibiting aqueous humor production in the ciliary body.^{60,61} Carbonic anhydrase inhibition has also been shown to vasodilate blood vessels in the retina and optic nerve of animals.⁶⁰ To enhance the effects of CAIs, NO moieties have been added to dorzolamide and brinzolamide, and preclinical studies have been conducted.^{61,62}

EMERGING DRUG DELIVERY METHODS

Sustained-Release Bimatoprost and Travoprost Implants

A phase 1/2 dose-ranging study described the efficacy of a sustained-release (SR) biodegradable implant containing bimatoprost.⁶³ At 16 weeks, eyes treated topically with bimatoprost had an average IOP reduction of 8.4 mm Hg. During this same time point, patients who received bimatoprost SR (6, 10, 15, or 20 μg) experienced an IOP reduction of 7.2, 7.4, 8.1, and 9.5 mm Hg, respectively. At 6 months, 71% of patients receiving bimatoprost SR did not require rescue or retreatment. The most common adverse event for both treatments was conjunctival hyperemia. Conjunctival hyperemia with an onset later than 2 days after the injection procedure occurred more often with topical bimatoprost (17.3%) than with the SR implant (6.7%).

There are phase 2 trials under way that are evaluating the safety and efficacy of intraocular travoprost implants compared with timolol.⁶⁴⁻⁶⁶ Both a biodegradable and a removable titanium implant are being investigated by their respective companies.^{67,68}

Bimatoprost Ring

The bimatoprost insert is a silicone ring loaded with bimatoprost. It is inserted around conjunctival fornices of the eye and replaced every 6 months.⁶⁹ A phase 2 randomized trial

compared the bimatoprost ring with timolol during a 6-month treatment period.⁶⁹ Intraocular pressure was reduced by 3.2 to 6.4 mm Hg and by 4.2 to 6.4 mm Hg with the bimatoprost ring and timolol, respectively. Adverse events were similar to those seen with other types of bimatoprost delivery methods. Alternative delivery methods such as this can help increase the poor adherence to POAG medication, which has been documented in patients receiving PGA and beta blocker therapy.^{70,71}

Key Take-Home Messages

- POAG is a complex and incompletely understood multifactorial disease
- Many risk factors are known; emerging risk factors may include OPP and CSF-P
- Treatments are in development, with new...
 - Mechanisms of action (NO, Rho kinase inhibition)
 - Sites of action (TM) and episcleral venous pressure
 - Drug delivery platforms (SR implants and conjunctival rings)
- Reduction in IOP remains the only established treatment goal

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CME POST TEST QUESTIONS

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See detailed instructions at **To Obtain AMA PRA Category 1 Credit™** on page 2.

- For the treatment of POAG, which of the following is the correct pairing of drug class and site of action?
 - Beta blocker: decreasing episcleral venous pressure
 - PGA: decreasing aqueous humor production
 - CAI: increasing uveoscleral outflow
 - Rho kinase inhibitor: increasing trabecular outflow
- How does LBN decrease IOP?
 - By decreasing aqueous production and increasing trabecular outflow resistance
 - By decreasing uveoscleral outflow and opening the iridocorneal angle
 - By decreasing trabecular outflow resistance and increasing uveoscleral outflow
 - By opening the iridocorneal angle and decreasing aqueous production
- Nitric oxide lowers IOP by decreasing:
 - Episcleral venous pressure
 - Resistance to trabecular outflow
 - Aqueous fluid production
 - Uveoscleral outflow
- Which therapy increases trabecular and uveoscleral outflow?
 - LBN
 - Timolol
 - Bimatoprost
 - Netarsudil
- A phase 3 trial compared an NO-donating formulation of latanoprost, LBN, with timolol. Which of the following is TRUE regarding this trial?
 - The study population excluded patients with ocular hypertension
 - The study design was open label
 - Patients treated with LBN achieved more IOP reduction than those treated with timolol
 - The most common treatment-emergent adverse events were mild to moderate and included conjunctival hyperemia in both treatment groups
- A phase 3 trial compared a Rho kinase inhibitor, netarsudil, with timolol. Which of the following is TRUE regarding this trial?
 - The study population included only patients with previously untreated glaucoma
 - Netarsudil was shown to be superior to timolol in patients with a baseline IOP < 25 mm Hg
 - Patients who had a baseline IOP < 25 mm Hg achieved an IOP reduction of ≥ 3.3 mm Hg after receiving netarsudil
 - Among patients with a baseline IOP < 25 mm Hg, timolol treatment lead to conjunctival hyperemia in < 5% of patients
- Which therapies promote smooth muscle relaxation of the TM?
 - Netarsudil and bimatoprost ring
 - NO-donating bimatoprost and CAIs
 - Latanoprost and netarsudil
 - LBN and netarsudil
- Which of the following decreases the risk for developing glaucoma?
 - Being Hispanic
 - Increasing intake of dietary nitrates
 - Having a corneal thickness < 555 μm
 - Having high myopia

ACTIVITY EVALUATION/CREDIT REQUEST

THE PRESSURE IS STILL ON! CURRENT AND EMERGING THERAPIES FOR MANAGING GLAUCOMA

To receive *AMA PRA Category 1 Credit™*, you must complete this **Evaluation** form and the **Post Test**. Record your answers to the **Post Test** in the Answer Box located below. Scan this completed page and return via e-mail to cme-nyee@nyee.edu or fax it to 212-870-8128. Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is e-mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

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OUTCOMES MEASUREMENT

Yes No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

- Outline the relationship between the sites of action and selection of IOP-lowering therapies
 - Discuss the role of nitric oxide in IOP regulation
 - Describe the mechanism of action of current and emerging topical glaucoma therapies
 - Evaluate the clinical relevance of safety and efficacy data for emerging topical therapies for the treatment of glaucoma
 - Assess traditional and emerging risk factors for progression in patients with ocular hypertension or glaucoma
- | | | | | | |
|--|---|---|---|---|---|
| | 5 | 4 | 3 | 2 | 1 |
| | 5 | 4 | 3 | 2 | 1 |
| | 5 | 4 | 3 | 2 | 1 |
| | 5 | 4 | 3 | 2 | 1 |
1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes
- | | | | | |
|--|---|---|---|---|
| | 4 | 3 | 2 | 1 |
|--|---|---|---|---|

Please describe the change(s) you plan to make: _____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face? _____

4. Number of patients with glaucoma I see per week
 0 1-5 6-10 11-25 More than 25

5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.

- Patient Care Practice-Based Learning and Improvement Professionalism
 Medical Knowledge Interpersonal and Communication Skills Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8