CME MONOGRAPH

PRESSURE MATTERS

NEW THERAPIES **IN THE MEDICAL MANAGEMENT OF GLAUCOMA**

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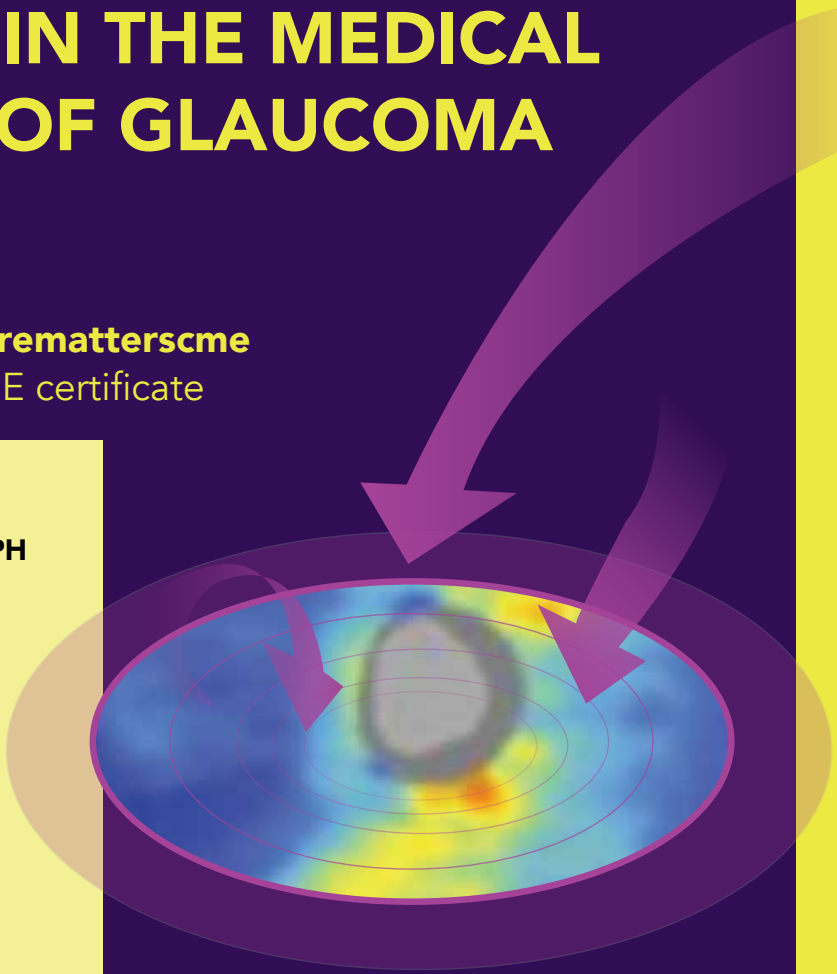

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ORIGINAL RELEASE: December 1, 2018

EXPIRATION: December 31, 2019

Jointly provided by **New York Eye and Ear Infirmary of Mount Sinai** and MedEdicus LLC

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ACTIVITY DESCRIPTION

Despite the variety of medical treatments for glaucoma, it is sometimes difficult to reach the target intraocular pressure (IOP) level in patients with this condition. Understanding the relationship between inflow and outflow pathways and how new treatments target alternative sites of action to decrease IOP is essential to provide optimal patient care. Toward this end, evidence-based treatment plans need to be updated to include new therapeutic options. Even with the availability of new treatments that can help preserve vision, some patients with glaucoma continue to remain nonadherent to treatment and should be counseled about the importance of adherence for their vision outcomes. The desired results of this activity are to update ophthalmologists on recent advances in the understanding of the pathophysiology and treatment of patients with glaucoma.

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:

- Describe how NO lowers IOP through the trabecular meshwork
- Recognize the relationship between aqueous humor dynamics and selection of therapies to lower IOP in patients with glaucoma
- Develop evidence-based treatment plans for achieving target IOP levels in patients with glaucoma
- Employ patient counseling strategies to ensure adherence to IOP-lowering medication schedules

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PRESSURE MATTERS

NEW THERAPIES **IN THE MEDICAL MANAGEMENT OF GLAUCOMA**

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INTRODUCTION

For the first time in more than 20 years, there are new classes of glaucoma medications with novel mechanisms of action for lowering intraocular pressure (IOP). Unlike the drugs that have been used for decades, latanoprostene bunod (LBN) and netarsudil both lower IOP by directly increasing the outflow of aqueous humor through the trabecular outflow pathway, which is the primary pathway through which aqueous humor exits the eye. These new drugs work at the root of the problem by improving the impaired trabecular outflow that leads to elevated IOP in eyes with glaucoma. In this educational activity, the mechanisms of action of LBN and netarsudil will be described, with a focus on their effects on aqueous humor dynamics. The development of evidence-based management of glaucoma in incorporating these new drugs to achieve and maintain target IOP in eyes with glaucoma will be discussed. Finally, strategies to improve patient adherence will be reviewed.

AQUEOUS HUMOR DYNAMICS: THE INS AND OUTS OF INTRAOCULAR PRESSURE

Intraocular pressure is determined by the balance of aqueous humor formation in the eye and the rate at which aqueous humor exits the eye. Aqueous humor is produced by the nonpigmented epithelial cells of the processes of the ciliary body.[1] Aqueous humor fills the posterior chamber, flows through the pupil, and fills the anterior chamber. The rate of aqueous humor formation is approximately 2.5 µL/min.[2] At this rate, aqueous humor in the anterior chamber is replaced approximately once every 100 minutes.

Aqueous humor leaves the eye through 2 distinct pathways. Most aqueous humor exits through the trabecular outflow pathway.[3] This involves passing through the 3 layers of the trabecular meshwork—uveal layer, corneoscleral layer, and juxtacanalicular layer—before entering Schlemm canal, where it passes into various collector channel orifices before entering distal collector channels and aqueous veins that are part of the episcleral venous system. The trabecular outflow pathway is also called the conventional outflow pathway.

A smaller proportion of aqueous humor exits the eye through the less well-characterized uveoscleral outflow pathway, or unconventional pathway.[4] To access this pathway, aqueous humor first crosses through the anterior face of the ciliary body, where it then passes between the muscle bundles of the ciliary body to access the suprachoroidal space, from which it exits the eye by passing through the sclera or by entering the choroid and exiting the eye through the vortex veins. The uveoscleral outflow pathway handles the minority of aqueous outflow and is less well understood than the trabecular pathway. It is the uveoscleral outflow pathway that is modified with the use of prostaglandin agents, taking a larger role in aqueous outflow.

Eyes with primary open-angle glaucoma (POAG) have elevated IOP primarily because of decreased aqueous humor outflow through the trabecular meshwork.[5] The rate of aqueous humor production is typically unchanged by glaucoma,[6-8] and the effect of uveoscleral outflow on the development of glaucoma remains controversial, in part because of the challenges of measuring uveoscleral outflow.[4]

ENHANCING TRABECULAR OUTFLOW IN GLAUCOMA

The 2 new drugs—LBN and netarsudil—act directly in the trabecular meshwork to increase trabecular outflow. Pilocarpine and other miotic drugs increase trabecular outflow indirectly by stimulating the ciliary muscle to tug on the scleral spur, mechanically stretching the meshwork and canal to open outflow channels. Latanoprostene bunod and netarsudil are the first drugs to act directly on trabecular meshwork tissue to decrease resistance to aqueous humor outflow.

Latanoprostene Bunod

Latanoprostene bunod is a novel molecule consisting of the prostaglandin analogue latanoprost and a nitric oxide (NO)-donating moiety. Upon instillation into the eye, the

molecule dissociates into its 2 active components. Latanoprost, a familiar prostaglandin analogue, lowers IOP by enhancing uveoscleral outflow. Nitric oxide, which has an interesting history leading up to its medical use, lowers IOP through direct action in the trabecular meshwork.[9]

Nitric oxide was discovered more than 200 years ago[10] and, until just the past few decades, was generally thought to be not important to human health and disease. In the 1970s, the well-known vasodilating effect that nitrates such as nitroglycerin have in the management of diseases such as angina pectoris was attributable to the liberation of NO from nitrates.[10] Soon thereafter, it was discovered that NO is synthesized by vascular endothelial cells,[11] leading to the realization that NO plays an important role in many biologic systems, including the cardiovascular and neurologic systems.

In healthy eyes, NO is synthesized in the endothelium of uveal vasculature, Schlemm canal, and the ciliary body.[12,13] Nitric oxide is known to increase trabecular outflow facility in the human anterior segment,[14] and NO donors lower IOP in animal models.[9] The mechanism by which NO lowers IOP is through relaxation of cells in the trabecular meshwork and Schlemm canal via rearrangement of actin-myosin interactions by decreasing myosin phosphorylation, which leads to increased aqueous humor outflow and IOP reduction **(Figure 1).**[12,15-17]

The effect of LBN on IOP has been evaluated in a number of key glaucoma studies. The pivotal phase 3 APOLLO and LUNAR studies randomized subjects with open-angle glaucoma or ocular hypertension in a 2:1 ratio to receive either LBN dosed once daily or timolol, 0.5%, dosed twice daily for 3 months.[18,19] Both studies were designed to evaluate the noninferiority of LBN to timolol as the primary end point. In a noninferiority trial, drug A is considered to be noninferior to drug B if drug A works at least as well, or better than, drug B. Intraocular pressure was measured at 8 AM, 12 PM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months after starting treatment. **Table 1** shows the IOP-lowering effects of the drugs in the APOLLO and LUNAR studies.[18,19] In the APOLLO study, LBN provided statistically significantly greater IOP reductions than did timolol at all 9 time points.[18] In the LUNAR study, LBN lowered IOP significantly more than did timolol at 8 out of 9 time points.[19] Both drugs were associated with low rates of ocular irritation and conjunctival hyperemia.[18,19] On the basis of these data, the US Food and Drug Administration approved LBN for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension.[20] The US Food and Drug Administration–approved dosage is 1 drop daily in the evening (qhs).

Additionally, the VOYAGER study was a phase 2 comparison of LBN with latanoprost **(Table 2)**.[21] In this dose-finding study, 4 concentrations of LBN, each dosed once daily at night, were compared with latanoprost, 0.005%, dosed once daily at night. Intraocular pressure was measured at 8 AM, 12 PM, and 4 PM at baseline and at 7, 14, and 28 days after starting treatment. Mean diurnal IOP reduction at the day 28 time point (the study's primary end point) was significantly greater in the LBN, 0.024%,

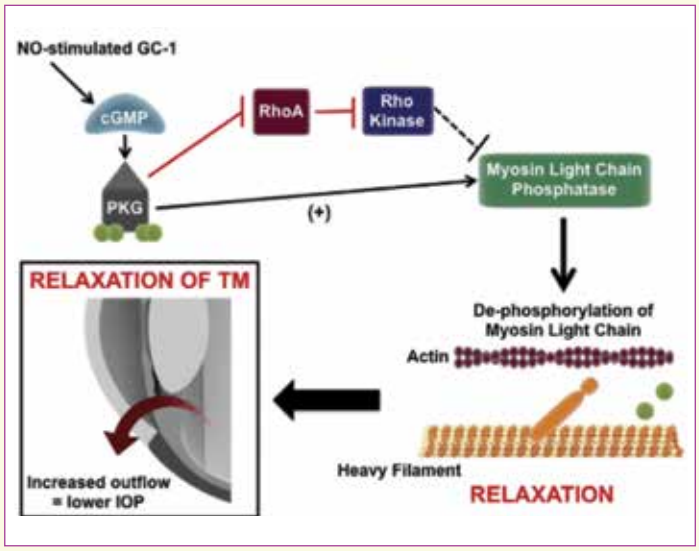

Figure 1. cGMP-mediated modulation of IOP through increase in aqueous humor outflow. Nitric oxide triggers production of cGMP by GC-1. cGMP activates PKG. Activated PKG can phosphorylate numerous targets with multiple downstream effects, including inhibition of Rho A, thus preventing inhibition of myosin phosphatase by Rho kinase. In addition to inhibition of Rho A, activated PKG can directly activate myosin light chain phosphatase. Subsequent dephosphorylation of the regulatory light chain of myosin by myosin light chain phosphatase prevents actin-myosin interaction, promoting cell relaxation. This in turn leads to a widening of the intercellular spaces in the juxtacanalicular TM and Schlemm canal, thus facilitating conventional aqueous humor outflow and lowering IOP.

Abbreviations: cGMP, cyclic guanosine monophosphate; GC-1, guanylate cyclase-1; IOP, intraocular pressure; NO, nitric oxide; PKG, protein kinase G; TM, trabecular meshwork.

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Table 1. Efficacy and Safety Outcomes of APOLLO and LUNAR Phase 3 Studies of LBN vs Timolol[18,19]

	APOLLO		LUNAR	
	LBN (n = 284)	**Timolol (n = 133)**	**LBN (n = 278)**	**Timolol (n = 136)**
Baseline IOP, mm Hg	26.7	26.5	26.6	26.4
Mean IOP reductions, mm Hg	8.0-9.0	6.5-8.0	7.5-8.8	6.6-7.9
Significance	LBN > timolol at all 9 time points ($P \leq .002$)		LBN > timolol at 8/9 time points ($P \leq .025$)	
Common side effects				
Eye irritation, %	3.9	2.2	7.2	4.4
Conjunctival hyperemia, %	2.8	1.5	4.4	0.7

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod.

Table 2. Efficacy and Safety Outcomes at Day 28 in the VOYAGER Phase 2 Study of LBN vs Latanoprost[21]

	LBN, 0.006% (n = 82)	LBN, 0.012% (n = 85)	LBN, 0.024%* (n = 83)	LBN, 0.040% (n = 81)	Latanoprost (n = 82)
Baseline IOP, mm Hg	26.1	26.25	26.0	26.0	26.15
Mean IOP reductions, mm Hg	7.8	8.3	9.0	8.9	7.8
Significance vs latanoprost	.913	.258	.005	.009	—
Common side effects					
Eye irritation, %	1.2	2.4	3.6	6.2	0
Conjunctival hyperemia, %	1.2	3.6	4.8	3.7	0

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod.

* Approved dose

group (the approved dose) than in the latanoprost group (9.00 mm Hg vs 7.77 mm Hg; *P* = .005). Although the concentration of latanoprost in each of the 4 LBN groups was greater than that in the latanoprost group, a previous study suggests that increasing latanoprost concentration does not increase efficacy.[22]

Netarsudil

Netarsudil is a novel drug in a new class of drugs known as Rho kinase inhibitors. Rho kinase is an enzyme that regulates the shape and movement of cells by acting on the cytoskeleton. In the eye, inhibition of Rho kinase leads to smooth muscle relaxation of both the trabecular meshwork and the episcleral veins. Thus, netarsudil acts to increase trabecular outflow by both increasing aqueous humor flow through the trabecular meshwork[23,24] and reducing downstream resistance to flow by decreasing the pressure within the episcleral venous system.[23] In addition to inhibiting Rho kinase, netarsudil also inhibits the actions of a molecule called norepinephrine transporter. In doing so, netarsudil increases adrenergic activity within the eye, which in turn suppresses aqueous humor production. Thus, netarsudil lowers IOP by up to 3 distinct mechanisms at 3 locations within the eye.

The effects of netarsudil on IOP were evaluated in a series of clinical trials. The ROCKET-1 and ROCKET-2 studies were phase 3 comparisons of netarsudil, 0.02%, dosed once daily (ROCKET-1 and ROCKET-2 studies) or twice daily (ROCKET-2 study only) and timolol, 0.5%, dosed twice daily for 3 months.[25] Both studies were designed to establish noninferiority of netarsudil to timolol as the primary end point. Intraocular pressure was measured at 8 AM, 10 AM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months after starting treatment. **Table 3** shows the efficacy and safety outcomes of these studies. In ROCKET-1, in the primary analysis in which baseline IOP was below 27 mm Hg, mean IOP reductions in the timolol group were greater than those in the netarsudil once-daily group. Criteria for noninferiority were not met. In a post hoc analysis of

Table 3. Efficacy and Safety Outcomes of ROCKET-1 and ROCKET-2 Phase 3 Studies of Netarsudil vs Timolol[25] and the Phase 2 Study of Netarsudil vs Latanoprost[28]

	ROCKET-1 (Eyes With IOP < 27 mm Hg)		ROCKET-1 (Eyes With IOP < 25 mm Hg)		ROCKET-2		Phase 2 Study	
	Netarsudil (n = 202)	Timolol (n = 209)	Netarsudil (n = 113)	Timolol (n = 124)	Netarsudil Once Daily (n = 251)	Timolol (n = 251)	Netarsudil, 0.02%* (n = 72)	Latanoprost (n = 77)
Baseline IOP, mm Hg	21.8-23.4	21.45-23.4	20.6-22.4	20.5-22.5	20.4-22.5	20.7-22.5	25.6	25.5
Mean IOP reductions, mm Hg	3.3-5.0	3.7-5.1	3.7-5.1	3.2-4.7	3.3-4.6	3.7-5.1	5.7	6.8
Significance	Netarsudil inferior to timolol		Netarsudil noninferior to timolol		Netarsudil noninferior to timolol		Netarsudil inferior to latanoprost	
Common side effects								
Conjunctival hyperemia, %	53.2	8.2	—	—	50.2	10.8	57.0	16.0
Conjunctival hemorrhage, %	13.3	0.5	—	—	14.7	0	6.0	0
Corneal verticillata, %	5.4	0	—	—	8.8	0.4	0†	0†

Abbreviation: IOP, intraocular pressure.

* Netarsudil, 0.02%, is the approved dose; additional doses were included in this study but not shown

† Short 28-day study precluded observation of corneal verticillata, which typically appears with longer dosing

eyes with baseline IOP below 25 mm Hg, netarsudil once daily was statistically noninferior to timolol. In ROCKET-2, only eyes with baseline IOP below 25 mm Hg were included in the primary analysis. In this subset of eyes, once-daily netarsudil was also statistically noninferior to timolol. Netarsudil was associated with a substantially higher rate of hyperemia compared with timolol and with the development of both conjunctival hemorrhages and corneal verticillata. In addition, the ROCKET-4 trial demonstrated noninferiority to timolol in patients with an IOP of up to < 30 mm Hg.[26] Safety data were consistent with observations in the ROCKET-1 and ROCKET-2 studies. The most common adverse event was hyperemia. These data led to the approval of netarsudil for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.[27] Its approved dosage is 1 drop daily in the evening (qhs).

In addition to these phase 3 studies, netarsudil was compared with latanoprost in a 28-day phase 2 study (also summarized in **Table 3**).[28] In this monotherapy study, subjects were randomly assigned to receive netarsudil or latanoprost, each dosed once daily. The primary end point was diurnal IOP reduction at day 28. At day 28, mean IOP reduction was 5.7 mm Hg for netarsudil and 6.8 mm Hg for latanoprost. In the statistical analysis, netarsudil was found to be inferior to latanoprost.

NORMAL-TENSION GLAUCOMA: AN OFTEN-OVERLOOKED DIAGNOSIS

In the United States, approximately 50% of patients with open-angle glaucoma have IOP ≤ 21 mm Hg at the time of diagnosis.[29] Likewise, the Barbados Eye Study found that in people of African descent, approximately 54% of eyes with newly diagnosed glaucoma have IOP ≤ 21 mm Hg.[30] In Asia, normal-tension glaucoma (NTG) is far more common: 50% to 90% of all glaucoma cases are NTG, with an IOP ≤ 21 mm Hg.[31] Still, it is not unusual to start therapy in these patients because their applanation IOP might appear to be in a "normal range", but other methods of checking IOP, such as pneumotonometry, often reveals a higher IOP. In addition, many of these patients reveal higher IOPs with further applanation testing.

Normal-tension glaucoma is diagnosed in the same manner as high-tension glaucoma, according to optic nerve and visual field damage. Without the red flag of elevated IOP, NTG will be detected on clinical examination only with a careful inspection of the optic nerve. Also, in the absence of elevated IOP, NTG becomes a diagnosis of exclusion, and a number of other conditions should be considered **(Table 4).**

Neurologic diseases can occasionally be confused with NTG, and the role of routine neuroimaging for cases of suspected NTG is often discussed. In fact, studies suggest that routine neuroimaging to rule out central nervous system lesions in eyes with NTG is generally nonproductive.[32] Instead, neuroimaging should be reserved for cases in which the clinical findings are more consistent with a central lesion than with glaucoma. These findings include optic nerve pallor rather than cupping, afferent

Table 4. Masqueraders of Normal-Tension Glaucoma

POAG with IOP fluctuations (including nocturnal elevations)
Thin central cornea with underestimation of IOP
Corneal refractive surgery with thinning and/or flattening of the cornea
Intermittent angle-closure glaucoma
Burned-out pigmentary glaucoma
Prior ocular trauma
Prior steroid use
Systemic medications that lower IOP (eg, beta blockers)
Central nervous system lesions

Abbreviations: IOP, intraocular pressure; POAG, primary open-angle glaucoma.

pupillary defects out of proportion to asymmetric cupping, color vision abnormalities, reductions in central visual acuity, visual field defects that respect the vertical meridian, and younger age.

Even though IOP is in the normal range in eyes with NTG, studies support the role of IOP reduction in reducing the risk of future progression. The Collaborative Normal-Tension Glaucoma Study randomized 145 patients with NTG to receive treatment or observation.[33,34] The goal of treatment was to achieve a 30% IOP reduction using any means available, except that beta blockers and adrenergic agonists were not allowed because of their potential deleterious effects on ocular blood flow. After up to 8 years of follow-up, glaucoma progression was noted in 35% of untreated eyes and in only 12% of treated eyes ($P < .001$).[34] This protection from progression came at a cost, however, because the rate of cataract formation was significantly higher in the treatment group than in the observation group (35% vs 14%; $P = .001$).[33] In a separate study, eyes with NTG were randomized to receive either brimonidine, 0.2%, or timolol, 0.5%, each dosed twice daily.[35] Over a 4-year follow-up period, visual field progression was noted in 9.1% of brimonidine-treated eyes vs 39.2% of timolol-treated eyes ($P < .001$). However, discontinuation rates with assigned therapy were high: 10% of patients in the timolol group and 30% of patients in the brimonidine group discontinued therapy during the follow-up period.

THE ROLE OF NEW DRUGS IN EYES WITH NORMAL-TENSION GLAUCOMA

How effective are LBN and netarsudil in eyes with glaucoma and IOP in the normal range? The JUPITER study evaluated LBN in 130 Japanese patients with ocular hypertension or POAG (including NTG).[36] Mean baseline IOP was 19.6 mm Hg—well within the normal range—in this single-arm, open-label study. Following 52 weeks of treatment, mean IOP was reduced by 22% ($P < .001$), and the most common adverse events were conjunctival hyperemia (17.7%), eyelash growth (16.2%), and ocular irritation/pain (11.5%/10%).

Netarsudil has also been evaluated in eyes with normal IOP. In a fellow-eye, placebo-controlled, randomized study, 11 healthy volunteers received netarsudil, 0.2%, once daily for 7 days in the

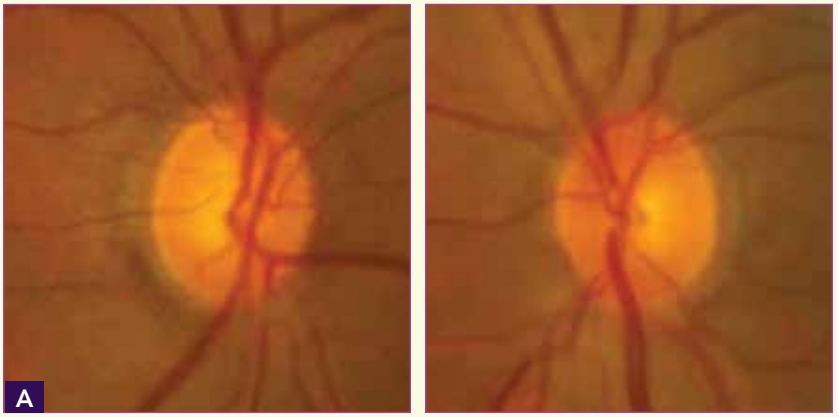
randomly selected study eye and placebo drops in the fellow eye.[23] Mean diurnal IOP (the average of IOP at 1 PM and 3 PM) was reduced from 17.0 mm Hg to 12.4 mm Hg in the netarsudil eyes (27%) and from 16.7 mm Hg to 16.0 mm Hg (7.2%) in placebo eyes ($P < .0001$). Conjunctival hyperemia was seen in all 11 netarsudil-treated eyes. The post hoc analysis of ROCKET-1 data in eyes with lower baseline IOP (range, 20.6-22.4 mm Hg) also demonstrated the IOP-lowering efficacy of netarsudil **(Table 3).**[25]

CASE 1. OCULAR HYPERTENSION OR GLAUCOMA?

From the Files of Donald L. Budenz, MD, MPH

A 71-year-old man seeks a second opinion for recently diagnosed ocular hypertension. His IOP values have ranged from 22 to 26 mm Hg prior to consultation, and observation—rather than treatment—was recommended. He is in good general health and takes no ocular or systemic medications. His mother had glaucoma.

On examination, his best-corrected visual acuity is 20/25 OU, with a small myopic correction. His IOP is 25 mm Hg OD and 26 mm Hg OS. His central corneal thickness (CCT) is 542 µm OD and 544 µm OS. He has moderate nuclear sclerotic cataracts in both eyes. His iridocorneal angles are wide open (Shaffer grade IV).



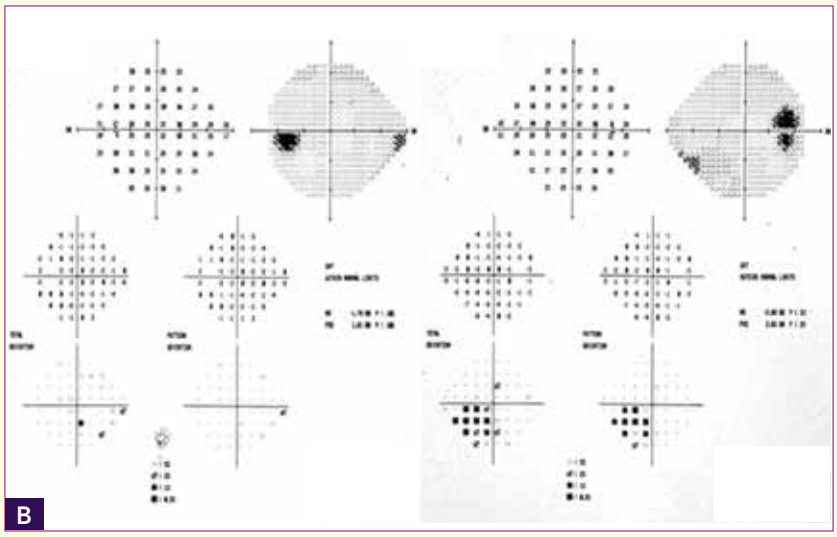


Figure 2. The optic nerves (A) and visual fields (B) of the patient presented in Case 1

The right optic nerve has a vertically elongated cup, with an estimated cup-to-disc ratio (CDR) of 0.6 vertically and 0.4 horizontally. The left optic nerve has a small, round cup, with a CDR of approximately 0.3 **(Figure 2A).** The visual field in the right eye is abnormal. The Glaucoma Hemifield Test is outside normal limits, and an inferior nasal step/arcuate scotoma is present. The visual field in the left eye is normal **(Figure 2B).**

This man has elevated IOP, characteristic optic nerve damage (vertical elongation of the optic cup), and typical visual field loss in the right eye. His diagnosis is POAG, and not ocular hypertension. Stereoscopic disc photographs were obtained, and a target pressure of ≤ 18 mm Hg or less was established.

From a peak untreated IOP of 26 mm Hg, an IOP reduction of ≥ 8 mm Hg is needed to achieve the target IOP. Well-established, first-line medical options include latanoprost and timolol. Latanoprost typically provides 6 to 8 mm Hg of IOP reduction when used as monotherapy, and timolol typically provides an IOP reduction in the 4- to 6-mm Hg range.[37] Both new agents—LBN and netarsudil—are approved for lowering IOP in ocular hypertension and in open-angle glaucoma.[20,27] Netarsudil typically provides 3 to 6 mm Hg of IOP reduction,[25,28] whereas LBN lowers IOP by 8 to 9 mm Hg on average.[18,19] Of these agents, latanoprost and LBN offer the best chance of reaching target IOP using a single medication.

CASE 2. GLAUCOMA MANAGEMENT AFTER VITREORETINAL SURGERY

From the Files of Ronald L. Fellman, MD

A 69-year-old man presents for glaucoma consultation. He has had POAG since 2000 and also has had a complicated past ocular history. In 2004, he underwent a scleral buckling procedure OD for a retinal detachment likely related to high myopia OU. In 2008, he underwent bilateral cataract surgery that was complicated OD, resulting in the placement of an anterior chamber intraocular lens. The procedure was uncomplicated OS, and a posterior chamber intraocular lens was placed. A prophylactic peripheral iridotomy was not performed at the time of surgery in the right eye—which is recommended when implanting an anterior chamber lens—and later the same year, the right eye had an attack of angle-closure glaucoma, which was treated with a peripheral iridotomy. In 2016, his right eye developed vitreomacular traction, with a macular wrinkle requiring a pars plana vitrectomy and membrane peel.

His current glaucoma regimen includes latanoprost OU daily, brinzolamide OU 3 times daily, the brimonidine/timolol fixed combination OU twice daily, and pilocarpine OD 3 times daily. He has previously undergone selective laser trabeculoplasty,

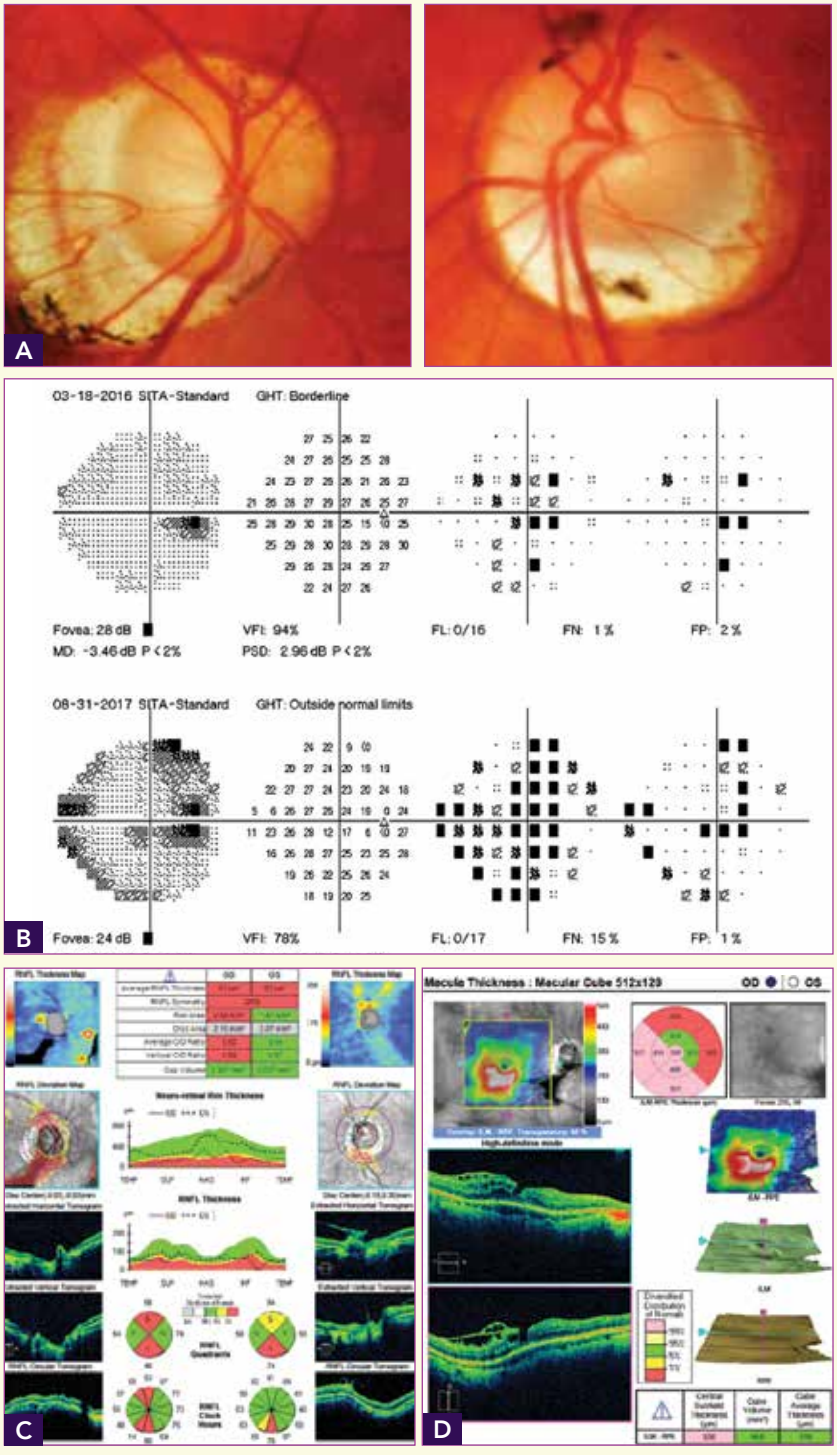


Figure 3. Right and left optic discs (A); visual field from the right eye showing change over time (B); and optical coherence tomography images of the retinal nerve fiber layer (C) and macula (D) of the patient presented in Case 2

micropulse cyclophotocoagulation, and 2 sessions of diode cyclophotocoagulation with the G-probe.

On examination, his visual acuity is 20/40 OD and 20/25 OS. He has mild inferonasal corneal edema OD, attributable to pseudophakic bullous keratopathy, with 4 clock hours of peripheral anterior synechiae. His IOP is 23 mm Hg OD and 17 mm Hg OS. On the basis of his optic nerve appearance—both clinically and by optical coherence tomography (OCT)—and his visual field status, his target IOP range was set at 18 to 21 mm Hg OU in 2015.

The optic disc photographs show significant peripapillary atrophy and tilting consistent with high myopia **(Figure 3A).** Although cupping can be difficult to judge in myopic nerves, the right eye clearly has more cupping than the left eye. The visual field in the right eye shows some change from 2016 to 2017 while maintained at a target IOP of 22 mm Hg **(Figure 3B).** It is unclear if this change in the field is attributable to glaucoma progression, corneal edema, macular wrinkling, or a combination of all 3. The retinal nerve fiber layer (RNFL) OCT shows significantly more loss in the right eye than in the left eye **(Figure 3C),** and the macular OCT reveals macular distortion in the right eye **(Figure 3D).**

This patient is just above target IOP in the right eye, and he might be progressing at this IOP level. He is currently receiving 5 classes of IOP-lowering medications, which, until recently, represented maximal medical therapy. His multiple vitreoretinal surgeries, coupled with 3 cyclophotocoagulation procedures, have resulted in conjunctival scarring that limits the likely success of any filtering procedures. One consideration when IOP is not controlled on maximal medical therapy is the issue of therapeutic nonadherence. Strategies for optimizing adherence to glaucoma medical therapy are discussed in **Sidebar: Optimizing Adherence to Glaucoma Medical Therapy.** To further lower his IOP in the right eye, therapeutic options include switching from latanoprost to LBN and adding netarsudil. He was switched from latanoprost to LBN and had a 3-point drop to 20 mm Hg OD. To achieve even further IOP reduction, netarsudil, 0.02%, was added to the right eye, resulting in a further 3-point drop to 17 mm Hg. This eye developed mild corneal verticillata that was not clinically significant.

CASE 3. PIGMENTARY GLAUCOMA IN A YOUNG PATIENT

From the Files of Donald L. Budenz, MD, MPH

A 40-year-old man was diagnosed 1 year ago with pigmentary glaucoma. His peak untreated IOP was in the low 30s. His paternal grandmother had glaucoma. A target IOP of 21 mm Hg—an approximate 30% reduction—was set, and latanoprost was started. For the next year, his IOP ranged from the high teens to the low 20s.

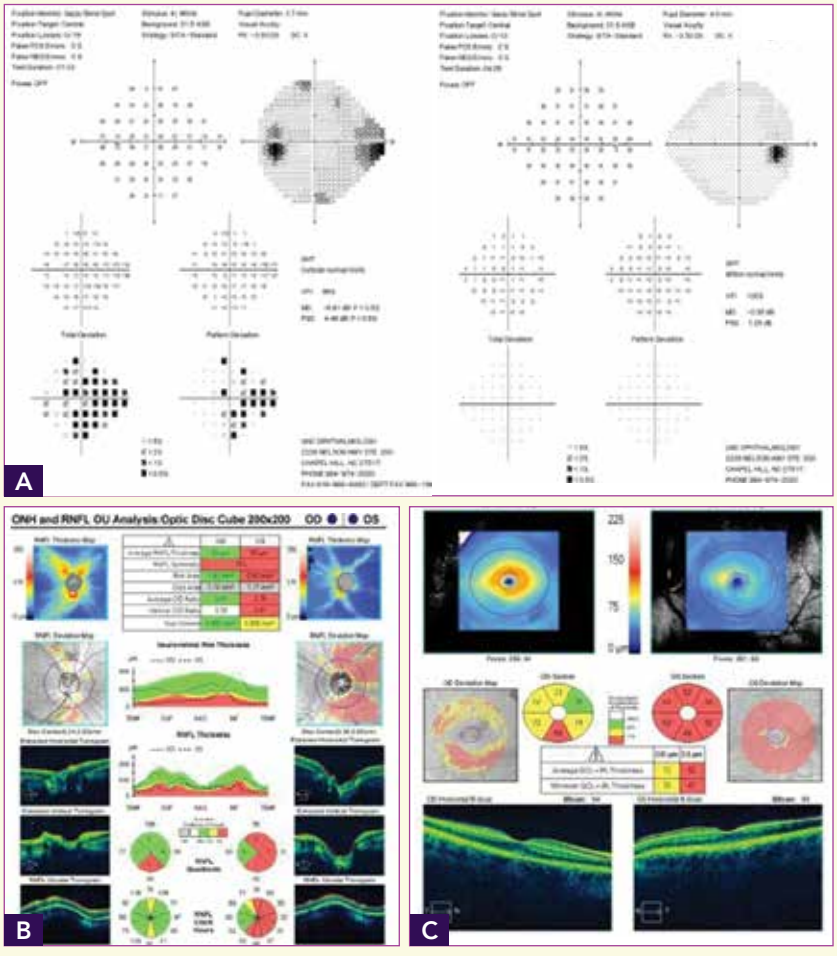


Figure 4. Visual fields (A) and optical coherence tomography images of the retinal nerve fiber layer (B) and macula (C) of the patient presented in Case 3

On the most recent examination, his visual acuity was 20/20 OU, with a -6.75 D myopic correction. Using latanoprost daily, his IOP is 15 mm Hg OD and 18 mm Hg OS. His CCT is 521 µm OD and 540 µm OS. His iridocorneal angles are wide open, with 3+ pigment OD and 4+ pigment OS. His CDR is 0.2 OD and 0.8 OS. **Figure 4** shows his visual fields and OCT images of the RNFL and macula. Compared with prior tests, both the visual field and the OCT RNFL have shown progression in the left eye over the past year, with IOP in the 18- to 21-mm Hg range.

This patient has pigmentary glaucoma, with a moderate visual field defect in the left eye. The first estimate of his target IOP was not low enough, as evidenced by his progression, with IOP at or below 21 mm Hg. Given his age, he will likely live with glaucoma for 30 or 40 more years, so effective control of his disease is critical to ensure that he does not suffer from visual dysfunction due to glaucoma during his lifetime. A new target IOP of < 16 mm Hg is set.

To achieve this new target IOP, a change in therapy is needed. There are several options to consider: latanoprost could be switched to LBN, netarsudil, or a fixed combination; or latanoprost could be maintained, and a second agent—a beta blocker, carbonic anhydrase inhibitor (CAI), netarsudil, or adrenergic agonist—could be added.

A target IOP of < 16 mm Hg calls for an additional 3 to 5 mm Hg of IOP reduction from the level attained with latanoprost. It is unlikely, according to data from clinical trials, that switching to LBN or netarsudil will provide this magnitude of additional IOP reduction. Because this otherwise healthy young patient lives an active lifestyle, beta blockers and fixed combinations containing beta blockers are a less desirable next step. The CAI brinzolamide is added 3 times daily because clinical trials suggest that CAIs are consistently more additive to prostaglandin analogues than are beta blockers or adrenergic agonists.[38-40] This drug is not covered by his insurance and he is unable to obtain it. Generic dorzolamide was prescribed for use 3 times daily; 1 month later, his IOP was 12 mm Hg OD and 14 mm Hg OS.

CASE 4. CONSIDERATIONS IN NORMAL-TENSION GLAUCOMA

From the Files of Ronald L. Fellman, MD

A 69-year-old man presents for an eye examination. His ocular history is significant for multiple refractive procedures, including radial keratotomy and photorefractive keratectomy in both eyes, and limbal-relaxing sutures in the right eye. He is pseudophakic in both eyes. His medications include propranolol for essential tremor, cyclosporine for ocular surface disease, and olopatadine for ocular allergies.

On examination, his visual acuity is 20/20 OU, with +1.50 D OU. His IOP is 14 mm Hg OD and 15 mm Hg OS, with CCT of 509 µm OD and 538 µm OS. His angles are open, although the right eye has 3 clock hours of peripheral anterior synechiae nasally. His CDR is 0.75 OD, with inferior thinning, and 0.8 OS, with both superior and inferior thinning. Laminar pitting is visible in both eyes. **Figure 5** shows his visual fields and OCT images of the RNFL.

In the right eye, there is loss of the inferior neuroretinal rim noted by both clinical examination and OCT, although the visual field is largely preserved. In the left eye, both superior and inferior rim loss is seen clinically and on OCT, and the visual field reflects this with a superior defect. The patient is not receiving any topical IOP-lowering medications, and the IOP is well within the normal range.

At first glance, this appears to be a case of NTG. However, several aspects of this case should be considered more fully. Both eyes have undergone multiple corneal refractive

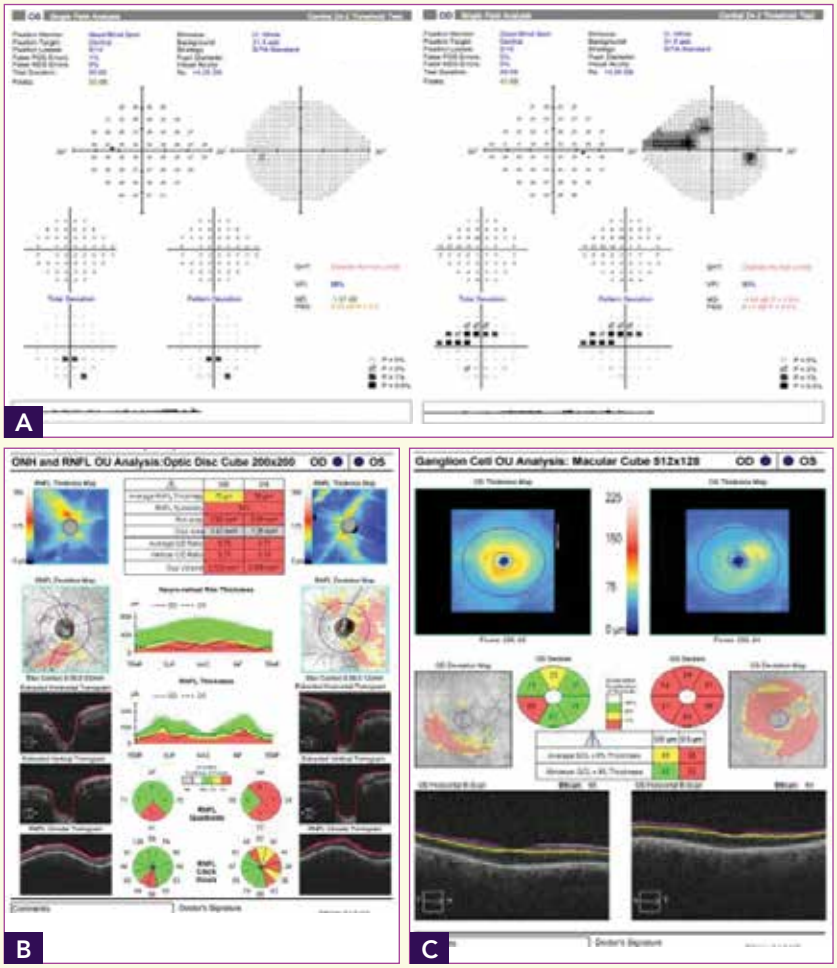


Figure 5. Visual fields (A) and optical coherence tomography images of the retinal nerve fiber layer (B) and macula (C) of the patient presented in Case 4

OPTIMIZING ADHERENCE TO GLAUCOMA MEDICAL THERAPY

Despite the proven benefit of medical intraocular pressure (IOP) reduction in lowering the risk of glaucoma progression, many patients with glaucoma do not adhere to their IOP-lowering medical regimens as prescribed. Nonadherent patients can be difficult to identify in routine clinical practice. The following strategies might improve adherence:

- **Education:** Patients with glaucoma should be educated that although largely asymptomatic until late in the disease, glaucoma can and often does lead to vision loss and blindness if not adequately treated. Patients should understand the importance of IOP reduction and also understand that their eye drops are what lower their IOP. A staff member should teach a proper medication instillation technique; a video demonstration might also be useful. Observing patients instilling drops can uncover physical limitations, such as poor grip strength or essential tremor.
- **Know the risk factors for nonadherence:** High out-of-pocket drug costs, side effects that disincentivize self-dosing, younger age, being a particular ethnicity, and poor overall health are all risk factors for nonadherence.
- **Simplify the regimen:** Fewer drops from fewer bottles improves the likelihood of adherence.
- **Probe for nonadherence:** In patients with suboptimal therapeutic responses, ask open-ended questions about adherence. Instead of asking, "Do you take your drops regularly?", consider asking, "We all miss medication doses from time to time. How many doses do you think you miss in a typical week?"

procedures, which are known to both thin and flatten the cornea. Each of these corneal changes is known to produce underestimation of IOP using Goldmann applanation tonometry.[41] In addition, the patient is using systemic propranolol, a beta blocker, which can also lower IOP. Together, these conditions might account for his low measured IOP, so the possibility that this is POAG cannot be ruled out.

Fortunately, the management of high-tension glaucoma and NTG are similar—IOP reduction. Guidelines based on expert consensus and clinical trials support an initial IOP reduction of approximately 30% for both POAG and NTG.[33,34,42] On this basis, a target IOP of 11 mm Hg is selected for the patient.

First-line therapy options for this patient include a prostaglandin analogue, timolol, LBN, and netarsudil. Clinical studies have demonstrated that latanoprost lowers IOP by 2 to 3 mm Hg in eyes with NTG.[43-45] Latanoprostene bunod has been shown in a prospective study to lower IOP by 4.3 mm Hg (22%) in Japanese eyes with normal baseline IOP.[36] Netarsudil lowers IOP by 4.6 mm Hg in healthy volunteers with normal baseline IOP.[23] As a result, either of the 2 new drugs—LBN or netarsudil—would be a reasonable first-line therapy for this patient.

SUMMARY AND TAKE-HOME POINTS

- Intraocular pressure is determined by the balance between aqueous humor production and aqueous humor outflow
  - Aqueous humor exits the eye through both the trabecular and uveoscleral outflow pathways
- Intraocular pressure is elevated in glaucomatous eyes because of impairment of aqueous humor outflow primarily through the trabecular outflow pathway
- Two new drugs—LBN and netarsudil—lower IOP by direct actions in the trabecular meshwork to improve trabecular outflow
  - Latanoprostene bunod is an NO-donating form of latanoprost; it lowers IOP by increasing uveoscleral outflow (via latanoprost) and trabecular outflow (via NO)
  - Netarsudil is a Rho kinase inhibitor and a norepinephrine transporter inhibitor; it lowers IOP by increasing trabecular outflow, reducing episcleral venous pressure, and reducing the production rate of aqueous humor
- Both LBN and netarsudil effectively lower IOP in eyes with low baseline IOP
  - Both drugs are approved for IOP reduction in eyes with ocular hypertension or open-angle glaucoma and can be used either first-line or as adjunctive therapy

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1. Components of the uveoscleral pathway include the ciliary body, suprachoroidal space, and ____.
   a. Ciliary processes
   b. Episcleral venous system
   c. Posterior chamber
   d. Choroid

2. Latanoprostene bunod lowers IOP by:
   a. Increasing uveoscleral outflow and reducing aqueous humor production
   b. Increasing uveoscleral and trabecular outflow
   c. Increasing trabecular outflow and decreasing episcleral venous pressure
   d. Decreasing aqueous humor production and decreasing uveoscleral outflow

3. In clinical trials, LBN lowered IOP by _____ mm Hg.
   a. 3.3 to 5.1
   b. 4.7 to 6.8
   c. 6.5 to 8.0
   d. 7.5 to 9.0

4. Common side effects of LBN include:
   a. Blurred vision and conjunctival hyperemia
   b. Eye irritation and conjunctival hyperemia
   c. Corneal verticillata and conjunctival hemorrhages
   d. Fatigue

5. Netarsudil lowers IOP by:
   a. Increasing trabecular outflow
   b. Decreasing episcleral venous pressure
   c. Decreasing aqueous humor production
   d. All the above

6. In clinical trials, netarsudil lowered IOP by _____ mm Hg.
   a. 1.4 to 3.5
   b. 3.3 to 5.1
   c. 4.7 to 6.7
   d. 5.5 to 8.0

7. Common side effects of netarsudil include:
   a. Blurred vision and conjunctival hyperemia
   b. Eye irritation and conjunctival hyperemia
   c. Corneal verticillata and conjunctival hemorrhages
   d. Bradycardia

8. Approximately _____ of open-angle glaucoma cases in the United States are of the normal-tension variety.
   a. 25%
   b. 50%
   c. 75%
   d. 90%

9. Neuroimaging should be considered for patients with suspected NTG who also have _____.
   a. 20/20 visual acuity
   b. Optic nerve cupping
   c. Pigment dispersion syndrome
   d. Abnormal color vision

10. Which of the following patients is most likely to be adherent to glaucoma therapy?
    a. A 70-year-old white male on prostaglandin analogue monotherapy, with insurance that covers his medications
    b. A 35-year-old man with juvenile open-angle glaucoma who is uninsured
    c. A 50-year-old African American woman using 6 drops from 3 bottles in each eye daily
    d. A newly diagnosed 75-year-old woman with essential tremor and early dementia who lives alone