LEARNING METHOD AND MEDIUM
This educational activity consists of a supplement and seven (7) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

CONTENT SOURCE
This continuing medical education (CME) activity captures content from an expert roundtable discussion.

ACTIVITY DESCRIPTION
Primary open-angle glaucoma is a leading cause of blindness, and although advances in pharmacologic and surgical treatments for glaucoma continue to grow, patients with glaucoma are still at risk for vision loss and blindness. Unfortunately, treatments to directly protect retinal ganglion cells from degeneration—the ultimate cause of vision loss—are lacking. New drugs, new fixed combinations of existing drugs, and new procedures constantly challenge the traditional treatment paradigm and are showing promise in lowering intraocular pressure (IOP) and slowing disease progression by multiple mechanisms of action. One explored mechanism involves nitric oxide signaling, which has been shown to have a role in the regulation of IOP. The purpose of this activity is to update ophthalmologists on the role of nitric oxide in the etiology and management of glaucoma.

TARGET AUDIENCE
This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
- Correlate the pathophysiologic factors contributing to glaucoma with sites of action for available treatments
- Discuss the role of nitric oxide in IOP regulation
- Describe the potential role of nitric oxide–based emerging therapeutics in the management of glaucoma

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INTRODUCTION
Currently, we have several therapies to lower intraocular pressure (IOP) and prevent progression and vision loss from glaucoma. The availability of highly effective medications with excellent safety profiles and convenient dosing permits the development of treatment regimens that are personalized to the needs and desires of each individual patient with this disease. Despite these therapeutic options, some people with glaucoma continue to develop visual loss and dysfunction attributable to the disease. The role of nitric oxide (NO) and its metabolic pathway as potential new therapeutic targets for glaucoma are described herein.

HISTORY OF NITRIC OXIDE AND ITS ROLES IN HUMAN PHYSIOLOGY
Joseph Priestley first discovered NO in the 1770s, and for the next 200 years, it was generally considered a toxic gas and air pollutant and disregarded with respect to human health. Over these next 2 centuries, several observations challenged this perception. The first was the use of nitroglycerin to relieve angina pectoris. The second was in the explosives industry, in which workers chronically exposed to nitroglycerin in the manufacture of trinitrotoluene developed short-term tolerance to nitrate-mediated vasodilation that wore off over the weekend, producing acute effects of tachycardia, dizziness, and headache from vasodilation upon reexposure. This constellation of symptoms was referred to as “Monday disease.” More recently, in 1977, NO was identified as an important component in the mechanism of action of nitrates in producing vasodilation, which explained its beneficial role in managing angina pectoris and shed light on the pathophysiology of Monday disease. A decade later, in 1987, endogenous NO synthesis was demonstrated...
in endothelial cells; thereafter, NO was rapidly recognized to have important regulatory roles in many biologic systems, including the cardiovascular and neurologic systems. Just 5 years later, the American Association for the Advancement of Science (publishers of Science) named NO the 1992 “Molecule of the Year.” The research that promoted this molecule from pollutant to Molecule of the Year in 15 short years earned 3 scientists the 1998 Nobel Prize in Medicine to honor their work in demonstrating NO’s role as a signaling molecule in the cardiovascular system.

Nitric oxide is synthesized by nitric oxide synthase (NOS), a cytochrome P-450 enzyme. There are 2 constitutive isoforms (neuronal NOS1 and endothelial NOS3) and an inducible isoform (NOS2). These isoforms are encoded by 3 different genes, each located on a different chromosome. Nitric oxide synthase produces NO in 2 steps by oxidizing L-arginine to L-hydroxyarginine and then to NO and citrulline.

Once synthesized, NO activates soluble guanylate cyclase (sGC), which then converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP is a second messenger (much like cyclic adenosine monophosphate) that modulates smooth muscle relaxation and vasodilation and many important biologic processes, such as platelet inhibition and cell growth and differentiation (Figure 1).

**Figure 1. Nitric oxide metabolic pathway and its physiologic effects.** Intracellular nitric oxide, synthesized by endothelial nitric oxide synthase, catalyzes the conversion of GTP to cGMP by guanylate cyclase. cGMP is a second messenger that signals a variety of downstream actions that leads to smooth muscle relaxation, inhibition of platelet adhesion/aggregation, and promotion of cell growth and differentiation. Reduction of cGMP levels can result in disease states related to the disruption of hemostasis.

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

**NITRIC OXIDE IN NONOCULAR PATHOPHYSIOLOGY**

Reduction of cGMP by inhibition of NO signaling plays a causal role in many human diseases and disorders related to vasoconstriction and/or vasospasm. These include angina pectoris, pulmonary hypertension, erectile dysfunction, thrombosis, and atherosclerosis. Strategies to increase cGMP levels have yielded numerous important treatments for diseases and disorders involving the NO pathway (Figure 2). Among these are the phosphodiesterase (PDE) inhibitors, which increase cGMP levels in cells by blocking its degradation. The resulting pharmacodynamic effect is smooth muscle relaxation. Phosphodiesterase inhibitors are commonly used to treat erectile dysfunction, in which they induce local vasodilation that in turn increases the blood supply to the penis. Other PDE inhibitors, such as roflumilast and cilomilast, and nonspecific PDE inhibitors, such as theophylline and theobromine, produce bronchodilation in the treatment of asthma. In addition, the sGC activator riociguat is approved for use in the management of pulmonary arterial hypertension. Other potential applications may include myocardial failure and endotoxic shock.

**Figure 2. Pharmacologic targets in the nitric oxide pathway.** The nitric oxide pathway has several actionable targets for pharmacologic management of disease states resulting from reduction in cGMP through various mechanisms. These include agents that increase endogenous levels of nitric oxide (LBN/glaucoma [experimental]), activate guanylate cyclase (riociguat/pulmonary hypertension), and increase cGMP levels by inhibiting PDE5 (sildenafil/erectile dysfunction). Abbreviations: ADP, adenosine diphosphate; ARG, arginine; ATP, adenosine triphosphate; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; GC, guanylate cyclase; GMP, guanosine monophosphate; GTP, guanosine triphosphate; LBN, latanoprostene bunod; NO, nitric oxide; P, phosphate; PDE5, phosphodiesterase type 5; PKG, protein kinase G.
NITRIC OXIDE IN THE HEALTHY EYE

Nitric oxide has important physiologic effects in the tissues that regulate both IOP and optic nerve head blood flow and plays an important physiologic role in the regulation of both of these dynamic parameters.

The optic nerve has a complex blood supply fed by 4 distinct circulatory beds, including the ophthalmic and posterior ciliary arteries as well as both the choroidal and retinal vascular beds. In the optic nerve head, NO donors decrease vascular resistance by relaxing smooth muscle, resulting in local vasodilation and increased optic nerve head blood flow.\(^{10,11}\) Conversely, impairment of the NO pathway reduces optic nerve blood flow, resulting in ischemia.\(^{12,13}\)

In a healthy eye, IOP is determined by the balance between aqueous humor production and outflow. Aqueous humor is produced by the nonpigmented epithelial cells of the ciliary body. Aqueous humor egress from the eye occurs via 2 distinct pathways: uveoscleral and canalicular. The uveoscleral outflow pathway is incompletely understood and involves passage of aqueous humor through the anterior uveal tract via the extracellular matrix–filled space between the ciliary muscle bundles into the suprachoroidal space, which then exits the eye via several routes, including choroidal veins and ocular lymphatics, as well as through the sclera. The canalicular pathway refers to the movement of aqueous humor through the trabecular meshwork (TM) to the Schlemm canal, with subsequent entry into the episcleral circulation. The TM is composed of extracellular matrix beams lined with trabecular cells. Like vascular smooth muscle cells, trabecular cells are contractile in nature.\(^{14}\) Trabecular cell contraction involves the interaction of actin and myosin and results in dense packing of the TM tissue, which reduces aqueous outflow. Resistance to outflow through the TM and inner wall of the Schlemm canal is the primary determinant of IOP. The beam cells of the inner TM are less important than the juxtacanalicular cells of the outer TM in regulating resistance to outflow.

Nitric oxide has important physiologic effects in several of the tissues relevant to the maintenance of IOP. Evidence for the role of NO in IOP regulation comes from several lines of research. Importantly, NOS3 is present in the uveal vascular endothelium, Schlemm canal, and ciliary body.\(^{15,16}\) Nitric oxide is known to increase trabecular outflow facility in the human anterior segment,\(^{17}\) and NO donors lower IOP in animal models.\(^{18}\) cGMP also increases outflow facility in live monkey eyes.\(^{19}\) Further, mice overexpressing NOS3 have lower IOP.\(^{20}\) NOS3 knockout mice (animals with no functional NOS3 gene and thus no endogenous NOS3) have elevated IOP,\(^{21}\) and sGC knockout mice exhibit both elevated IOP and optic nerve degeneration.\(^{22}\) The mechanism by which NO lowers IOP is via inhibition of actin-myosin interactions, which leads to relaxation of cells in the TM and Schlemm canal and subsequent enhanced aqueous outflow and IOP reduction.\(^{23,24}\)

NITRIC OXIDE IN THE GLAUCOMATOUS EYE

There is significant evidence that NO pathway dysfunction plays a causal role in the pathophysiology of primary open-angle glaucoma (POAG). In the optic nerve head, the NO system promotes vasodilation and increased blood flow to this important tissue bed. Conversely, inhibition of the NO pathway would be expected to reduce optic nerve head blood flow.

Evidence for these hypotheses in humans has been reported. In a clinical trial involving 12 patients with glaucoma and 12 healthy subjects, NOS inhibition accomplished by intravenous administration of a known inhibitor of NOS reduced optic nerve head blood flow in healthy eyes more than in glaucomatous eyes (\(P = .03\)),\(^{25}\) suggesting that the NO pathway is already impaired in glaucomatous eyes.

Support for the role of NO pathway impairment in IOP regulation comes from several distinct lines of research. L-arginine levels are high in the aqueous humor of patients with glaucoma\(^{26}\) and in the vitreous humor of monkeys with experimental glaucoma.\(^{27}\) Further, NO levels are low in the aqueous humor of patients with glaucoma.\(^{28,29}\) Additionally, NOS3 gene variants have been described in relation to POAG in many studies.\(^{30-32}\)

Other data support a role for impaired NO signaling in the pathophysiology of glaucoma. Acetylcholine (ACh) is known to mediate vasodilation via the generation of NO. Therefore, ACh delivered to healthy subjects would be expected to increase blood flow via NO signaling, whereas a reduced or absent increase in blood flow would be expected in subjects with impairment of the NO signaling pathway. In a pharmacologic intervention study, an
increase in forearm bl

ood flow was markedly attenuated in patients with untreated normal-tension glaucoma compared with controls. Likewise, peripheral limb ischemia should induce brachial artery vasodilation, but this response is impaired in patients with open-angle glaucoma across the spectrum of IOP.

These studies suggest an underlying impairment of the NO pathway in these patients.

NITRIC OXIDE PATHWAY AS A THERAPEUTIC TARGET IN GLAUCOMA

In light of the data supporting the role of impaired NO signaling in open-angle glaucoma, it is reasonable to investigate potential therapeutic targets within the NO signaling pathway that might prove effective in the treatment of glaucoma. The NO pathway represents a novel therapeutic target for glaucoma, and an NO-based therapy would offer a unique mechanism of action among existing treatment options. Multiple potential approaches are currently being investigated. Among these, agonists of sGC are being evaluated to increase production of cGMP, which results in vasodilation and increased outflow facility. Dietary supplementation with L-arginine represents a potential upstream intervention for conditions associated with NO pathway impairment. Such an approach may have value in favorably modulating endothelial dysfunction associated with diabetes, smoking, and obesity, although evidence to date is limited to animal and early clinical studies.

An analysis of the Nurses’ Health Study and
Dr Pasquale: First, we need to demonstrate that topically applied NO-donating drugs reach the retina surface at a concentration that achieves retinal vascular reactivity. Perhaps this type of research can be performed in animals and ex vivo preparations of retinal vascular tissues. Further, if disc hemorrhages are really a manifestation of impaired retinal vascular regulation, and assuming that an NO-donating therapy may enhance retinal vascular NO signaling, then it will be interesting to see if a drug like LBN reduces the frequency of disc hemorrhages, a biomarker that is highly correlated with disease progression.

Dr Buys: Because NO will not preferentially increase optic nerve head blood flow, but blood flow to any vascular tissue that the NO donor reaches, one would have to consider ocular hyperemia as a possible side effect, particularly with topically applied therapies.

Dr Stamer: Given potential issues, such as ocular penetration and topical side effects, we may need to develop a novel drug or delivery method to optimize the balance between efficacy and safety.

Dr Weinreb: One needs to know whether the NO from the topical medication is achieving biologically active levels at the retina and optic nerve head. One also needs to know that there is optic nerve (and retina) vasodilation, and that the vasodilation is beneficial to the disease outcome. This would require a clinical trial that would follow disease markers (e.g., visual fields and retinal nerve fiber layer thickness) over time.

Health Professionals Follow-up Study suggests that higher dietary nitrate intake may be related to a lower incidence of POAG, especially the subtype categorized by early paracentral visual field loss. An alternate approach is to increase intraocular NO directly, for example, via NO donor compounds. One such compound is nitradiol, an adrenergic receptor antagonist with an NO-donating moiety. Nitradiol is approved in Japan for the reduction of IOP in patients with glaucoma. Nitradiol is neuroprotective in animal models of glaucoma and was the subject of a human clinical trial in Japan to evaluate its ability to confer neuroprotection in normal-tension glaucoma. In this study, patients with normal-tension glaucoma randomly received either timolol, 0.5%, or topical nitradiol, 0.25%, twice daily for 36 months. These drugs are known to provide comparable IOP reduction. The primary end point was visual field progression, with a hypothesis that if nitradiol provides neuroprotection in addition to IOP reduction, then visual field progression should be less in the nitradiol group than in the timolol group. Both drugs lowered IOP comparably, with similar overall rates of visual field progression. However, a subsequent subgroup analysis revealed a statistical advantage of nitradiol over timolol in visual field progression, as measured by the corrected pattern standard deviation and by the average total deviation in the superior central subfield of the visual field (P ≤ .001).

Q: Should we be encouraging our patients with glaucoma to consume more nitrate-rich diets?

Dr Pasquale: Certainly nitrates derived from green-leafy vegetables have no downsides and have much in the way of potential health benefits. The reason it might be helpful in POAG is because of the nitrate-nitrite-NO cycle. Vegetable-derived nitrates are safely converted to NO via this pathway and serve as an exogenous source of NO. Theoretically, such a source of NO can be readily delivered to the TM and optic nerve. Our research showed that dietary nitrates from green-leafy vegetables were associated with a reduced risk of incident POAG, especially for cases with early paracentral visual loss. We think the latter finding is interesting because patients with impaired NO signaling may be particularly prone to paracentral vision loss. Our results were consistent with those of the Study of Osteoporotic Fractures, in which > 1 serving of kale or collard greens per week was associated with a reduced risk of glaucoma. Of course, these are observational studies and not randomized clinical trials. More study is needed to prove that consuming more nitrates from vegetable sources benefits patients with glaucoma.

Dr Kaufman: These are all excellent points. However, there remains the need for further research to establish both that NO-donating compounds, such as LBN, do have effects on optic nerve head blood flow and that such effects are clinically beneficial in glaucoma.

Q: Should we be encouraging our patients with glaucoma to consume more nitrate-rich diets?

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events were similar in nature and frequency in both groups and included blepharitis, keratitis, ocular hyperemia, and conjunctivitis.\textsuperscript{41} In a separate study, topical nipradilol was shown to improve optic nerve head blood flow.\textsuperscript{44} Taken together, these results suggest neuroprotection as an additional mechanism of action beyond IOP reduction for nipradilol in human glaucoma, although additional research is needed to explore these preliminary observations more fully.

Latanoprostene bunod is another NO-donating drug and prodrug that is metabolized to latanoprost and an NO molecule by ocular esterase enzymes.\textsuperscript{19} Preclinical studies evaluated the effects of LBN vs latanoprost alone on human TM cell contractility and the NO-cGMP signaling pathway.\textsuperscript{45} In these studies, LBN significantly increased cGMP levels and reduced TM cell contractility compared with latanoprost. In a nonhuman primate model of glaucoma, LBN lowered IOP more than an equimolar dose of latanoprost did (35% and 25%, respectively).\textsuperscript{46}

In a phase 2 study, LBN provided an approximately 1- to 1.5-mm Hg greater IOP reduction than did latanoprost ($P \leq .009$).\textsuperscript{47} Results from a phase 3 clinical trial of LBN have been reported recently.\textsuperscript{48} In this randomized, multicenter, double-masked study, 420 patients with either ocular hypertension or POAG were randomized to receive either LBN, 0.024%, every evening or timolol, 0.5%, twice daily for 3 months. The primary outcome measure was postbaseline IOP measured at 8 AM, 12 PM, and 4 PM at weeks 2 and 6 and month 3. The mean IOP at all 9 time points was significantly lower with LBN than with timolol ($P \leq .002$). In this study, significantly more patients treated with LBN achieved an IOP of $\leq 18$ mm Hg and a $\geq 25\%$ reduction in IOP than did those treated with timolol. The most common treatment-emergent adverse events were mild to moderate and included eye irritation upon instillation and conjunctival hyperemia, both of which were seen more frequently in the LBN group. There was 1 instance of severe eye pain in the timolol group. The investigators concluded that LBN, 0.024%, once daily was safe and effective, with significantly greater IOP-lowering effects than timolol. If LBN should garner approval by the US Food and Drug Administration, it would represent the first new drug with a novel mechanism of action since the debut of latanoprost in the mid-1990s.

Other well-established IOP-lowering agents are under investigation as potential NO donors. For example, an NO-donating formulation of bimatoprost is currently in development. In various animal models of glaucoma, this formulation produced mean IOP reductions on the order of 5 to 8 mm Hg in rabbits, dogs, and monkeys, in each case in excess of bimatoprost alone.\textsuperscript{49} Similarly, NO-donating formulations of the carbonic anhydrase inhibitors dorzolamide and brinzolamide lowered IOP in animal models more effectively than did the isolated carbonic anhydrase inhibitor molecules alone.\textsuperscript{50}

**CONCLUSION**

Glaucoma is a multifactorial disease with a complex pathophysiology and many known risk factors. Reduction of IOP remains the only established therapy. Intracocular pressure regulation is incompletely understood and involves many diverse physiologic pathways. A better understanding of the NO-cGMP pathway in human health and disease has resulted in novel therapeutic targets for many disease states, including glaucoma. The NO-cGMP pathway plays a role in the regulation of both optic nerve head blood flow and IOP, both of which are critically important in the glaucomatous disease state. The NO-donating molecule nipradilol, approved in Japan for the treatment of glaucoma, provides a proof of concept for this novel class of medications. The NO donor LBN shows significant promise as a novel therapeutic agent for glaucoma. Latanoprostene bunod and other emerging drugs have the potential to alter clinical glaucoma management in the near future, providing ever more tools to enhance the individualization of glaucoma therapy for our patients.
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1. One of the first diseases in which NO served as a therapeutic target was:
   a. Cancer
   b. Angina pectoris
   c. Cerebrovascular accidents
   d. Multiple sclerosis

2. Nitric oxide’s physiologic effect results in:
   a. Tachycardia
   b. Lipid metabolism
   c. Smooth muscle relaxation
   d. Norepinephrine reuptake

3. Patients with POAG might exhibit which of the following abnormalities?
   a. Increased aqueous humor level of cGMP
   b. Enhanced vasodilatory response to intravenous ACh
   c. Failure of vasodilation to peripheral limb ischemia
   d. All the above

4. Nitric oxide lowers IOP by which of the following mechanisms?
   a. Decreasing episcleral venous pressure
   b. Decreasing aqueous fluid production
   c. Increasing uveoscleral outflow
   d. Increasing trabecular outflow

5. Which of the following ocular structures is NOT relevant to the trabecular outflow pathway?
   a. Juxtacanonical TMT
   b. Schlemm canal
   c. Corneal endothelium
   d. Episcleral blood vessels

6. A phase 3 trial compared an NO-donating formulation of latanoprost, LBN, with timolol. Which of the following is FALSE regarding this trial?
   a. The patient population included patients with ocular hypertension and glaucoma
   b. The mean IOP at all 9 time points was lower with LBN than with timolol, but the results were not statistically significant
   c. More patients treated with LBN achieved an IOP of ≤ 18 mm Hg and a ≥ 25% reduction in IOP than did those treated with timolol
   d. The most common treatment-emergent adverse events were mild to moderate and included eye pain upon instillation in both treatment groups, with 1 case of severe eye pain in the timolol group

7. Which of the following regarding dietary nitrates is FALSE?
   a. They are found in green-leafy vegetables
   b. They have many systemic health benefits
   c. Epidemiologic studies suggest that a nitrate-rich diet may be associated with a reduced risk of incident POAG
   d. One serving of kale or collards per month can lower IOP
THE ROLE OF NITRIC OXIDE IN GLAUCOMA

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• Correlate the pathophysiologic factors contributing to glaucoma with sites of action for available treatments
• Discuss the role of nitric oxide in IOP regulation
• Describe the potential role of nitric oxide-based emerging therapeutics in the management of glaucoma

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. 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  ☐ Medical Knowledge  ☐ Interpersonal and Communication Skills

☐ Practice-Based Learning and Improvement  ☐ Professionalism  ☐ Systems-Based Practice

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

______________________________________________________________________________________________________________

ADDITIONAL COMMENTS

______________________________________________________________________________________________________________

POST TEST ANSWER BOX

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