LEARNING METHOD AND MEDIUM
This educational activity consists of a supplement and eight (8) 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 1.0 hour to complete.

CONTENT SOURCE
This continuing medical education (CME) activity captures content from an expert roundtable discussion held on August 25, 2016.

ACTIVITY DESCRIPTION
Therapy to lower intraocular pressure effectively reduces the risk of glaucoma progression. The rate of nonadherence with therapy remains high. Therapeutic nonadherence is a complex and multifactorial issue that is influenced by factors attributable to the physician, patient, and medication. All medications have side effects, and tolerability issues can contribute to nonadherence if patients perceive that the disadvantages of therapy outweigh the benefits of controlling a disease that is often asymptomatic. Therefore, the selection of initial and additional therapy should consider the potential for tolerability issues that may adversely affect adherence. Novel therapies in late-stage clinical development will offer innovative mechanisms of action and unique risk/benefit profiles. The purpose of this educational activity is to update ophthalmologists on the prevalence of and contributors to patient nonadherence to glaucoma treatments, potential methods of addressing nonadherence, and emerging medications with novel mechanisms of action for managing glaucoma.

TARGET AUDIENCE
This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
1. Counsel patients on optimal administration and adherence strategies
2. Describe the effect of tolerability of glaucoma medications on patient adherence
3. Describe the mechanism of action of current and emerging topical glaucoma therapies

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of New York Eye and Ear Infirmary of Mount Sinai and MedEdicus LLC. The New York Eye and Ear Infirmary of Mount Sinai is accredited by the ACCME to provide continuing medical education for physicians.

In July 2013, the Accreditation Council for Continuing Medical Education (ACCME) awarded New York Eye and Ear Infirmary of Mount Sinai “Accreditation with Commendation,” for six years as a provider of continuing medical education for physicians, the highest accreditation status that can be awarded by the ACCME.

AMA CREDIT DESIGNATION STATEMENT
The New York Eye and Ear Infirmary of Mount Sinai designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

GRANTOR STATEMENT
This continuing medical education activity is supported through an unrestricted educational grant from Inotek Pharmaceuticals Corporation.

DISCLOSURE POLICY STATEMENT
It is the policy of New York Eye and Ear Infirmary of Mount Sinai that the faculty and anyone in a position to control activity content disclose any real or apparent conflicts of interest related to the topic of this educational activity, and also disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentation(s). New York Eye and Ear Infirmary of Mount Sinai has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Full disclosure of faculty/planners and their commercial relationships, if any, follows.

DISCLOSURES
Robert D. Fechtner, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: Alcon; Bausch & Lomb Incorporated; and Inotek Pharmaceuticals Corporation; Contracted Research: Alcon; and Pfizer Pharmaceuticals Corporation.

James C. Tsai, MD, MBA, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: Aerie Pharmaceuticals, Inc, and Inotek Pharmaceuticals Corporation.

NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI
PEER REVIEW DISCLOSURE
Joseph F. Panarelli, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: Allergan

EDITORIAL SUPPORT DISCLOSURES
Diane McArtle, PhD; Cynthia Tornaylayf, RD, MBA, CHCP; Kimberly Cobrin, CHCP; Barbara Aubel; and Michelle Ong have no relevant commercial relationships to disclose.

DISCLOSURE ATTESTATION
The contributing physicians listed above have attested to the following:
1) that the relationships/affiliations noted will not bias or otherwise influence their involvement in this activity;
2) that the physician or practice lists of companies with whom they have relationships/affiliations will be supported by the best available evidence or, absent evidence, will be consistent with generally accepted medical practice; and
3) that all reasonable clinical alternatives will be discussed when making practice recommendations.

OFF-LABEL DISCUSSION
This CME activity includes discussion of unlabeled and/or investigative uses of drugs. Please refer to the official prescribing information for each drug discussed in this activity for FDA-approved dosing, indications, and warnings.

For Digital Editions
System Requirements:
If you are viewing this activity online, please ensure the computer you are using meets the following requirements:
• Operating System: Windows or Macintosh
• Media Viewing Requirements: Flash Player or Adobe Reader
• Supported Browsers: Microsoft Internet Explorer, Firefox, Google Chrome, Safari, and Opera
• A good Internet connection

New York Eye and Ear Infirmary of Mount Sinai Privacy & Confidentiality Policy
http://www.nyee.net/health-professionals/cme-enduring-activities

CME Provider Contact Information
For questions about this activity, call 212-979-4383.

TO OBTAIN AMA PRA CATEGORY 1 CREDIT™
To obtain AMA PRA Category 1 Credit™ for this activity, read the material in its entirety and consult referenced sources as necessary. Complete the evaluation form along with the post test answer box within this supplement. Remove the Activity Evaluation/Credit Request page from the printed supplement or print the Activity Evaluation/Credit Request page from the Digital Edition. Return via mail to Kim Corbin, Director, ICMEd, New York Eye and Ear Infirmary of Mount Sinai, 485 Madison Avenue, 17th Floor, New York, NY 10022 or fax to (212) 353-5703. Your certificate will be mailed to the address you provide on the Activity Evaluation/Credit Request form. Please allow 3 weeks for Activity Evaluation/Credit Request forms to be processed. There are no fees for participating in and receiving CME credit for this activity.

Alternatively, we offer instant certificate processing and support Green CME. Please take this post test and evaluation online by going to http://tinyurl.com/glaucotox. Upon passing, you will receive your certificate immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. Upon registering and successfully completing the post test, your certificate will be made available online and you can print it or file it.

DISCLAIMER
The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of New York Eye and Ear Infirmary of Mount Sinai, MedEdicus LLC, Inotek Pharmaceuticals Corporation, EyeNet, or the American Academy of Ophthalmology.

Visit http://tinyurl.com/glaucotox for online testing and instant CME certificate.
GLAUCOMA MEDICAL THERAPY
OCULAR TOLERABILITY, ADHERENCE, AND PATIENT OUTCOMES

GOALS OF GLAUCOMA THERAPY
The goal of glaucoma therapy is to prevent progression of the disease. The approach to this goal is to lower intraocular pressure (IOP) because it is considered a risk factor for glaucoma and its progression, and is the only established therapy for glaucoma. Numerous clinical trials have demonstrated that IOP reduction lowers the risk of disease progression. Other independent risk factors for glaucoma progression include older age, thinner central corneas, bilateral disease, and disc hemorrhages.

The optimal IOP reduction necessary to halt progression differs among patients and is not easily determined prospectively. Risk assessment allows identification of the patients most at risk. These patients may benefit from greater IOP reductions than those whose risk of progression is lower.

Many major clinical trials have demonstrated that lowering IOP can prevent or delay the development of glaucoma in eyes with ocular hypertension, as well as prevent progression in both low-pressure and high-pressure open-angle glaucoma. The benefit of IOP reduction is consistent, whether it is accomplished by medications, laser therapy, or surgery.

Dr Parrish: How do we best assess whether therapy is effective in accomplishing this goal? If I use the target IOP approach, in which I determine a narrow range of IOP within or below which I feel progression is unlikely to occur, I determine each patient's target IOP range on the basis of his/her individual risk factors and prior clinical course.

Dr Realini: This is a common approach and represents the best standard, according to our current knowledge. However, setting a target IOP necessitates some guesswork on our part, and we do not know which of our patients are well controlled, except in retrospect. The well-controlled patients are the ones who do not progress under therapy. We cannot know with certainty whether a patient is well controlled, in part, because we do not fully understand the optimal IOP profile that halts the disease. We lack clarity on the specific IOP behaviors that lead to optic nerve damage progression, so we cannot design interventions to achieve those proactively. Future research may help clarify the specific goals of therapy. In the meantime, we lower peak IOP using the target IOP approach, and that in turn lowers mean IOP and variability.

Dr Tsai: In the face of these uncertainties, the target pressure approach remains important. I agree that a range is better than a single number. We should also avoid rigid enforcement of our target. If the patient's IOP is 1 to 2 mm Hg above target, we have to ask whether the incremental risks associated with the next intervention outweigh the benefits of additional therapy.

Dr Parrish: Having acknowledged that we lack the tools to fully characterize IOP and its response to therapy, we can all agree that IOP lowering is the only option to slow or halt progression. Once we have initiated medical therapy in a patient with newly diagnosed primary open-angle glaucoma (POAG), what are the factors that affect the quality of IOP control achieved by our intervention?

Dr Realini: Selection of therapy dictates the quality of IOP reduction achieved. Ideally, a glaucoma drug would lower mean IOP, collapse variability, and provide 24-hour IOP reduction, while posing no serious safety or tolerability issues, and all this at a reasonable cost. Not every available drug offers all of these qualities, and no drug can provide these qualities if it is not taken by the patient.

Figure 1. Intraocular pressure is highest at night in the supine position among patients with glaucoma.

Republished with permission of Association for Research in Vision and Ophthalmology, from Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes, John H. K. Liu, Xiaoyan Zhang, Daniel F. Kripke, Robert N. Weinreb, 44, 2003; permission conveyed through Copyright Clearance Center, Inc.

Dr Fechtner: Physicians who manage diabetes and systemic hypertension have the benefit of tools with which patients can self-measure the biologic parameter of interest, whether it is blood glucose levels or systemic blood pressure. We lack such tools in glaucoma. Patients cannot easily and safely measure their IOP at home, so we are limited to the measurements we obtain in the office during limited hours of the day. Our sampling rate is low; because of this, we likely do not have a complete picture of our patients' true IOP behavior. We often have to make decisions in the face of uncertainty.

“Selection of therapy dictates the quality of IOP reduction achieved.”
- Dr Realini

“...I determine each patient's target IOP range on the basis of his/her individual risk factors and prior clinical course.”
- Dr Parrish

Nonadherence
Numerous studies have demonstrated that patients with glaucoma tend to adhere suboptimally to glaucoma therapy. Nonadherence takes several forms. Some patients do not take their medication, either intentionally or because of chronic forgetfulness. Others are motivated and take their medication, but technique issues limit effectiveness (eg, missing the eye or instilling multiple drops too closely together). Such patients can often be identified by poor response to therapy. Others, more problematically, only take their medication before scheduled office visits. Such nonadherence is more difficult to detect and may only manifest with progression. Others habitually miss appointments, depriving providers of the opportunity to detect both nonadherence and the resulting progression.

Visit http://tinyurl.com/glaucomatherapy for online testing and instant CME certificate.
Barriers to adherence in glaucoma have been evaluated in many studies and include factors related to the patient, to the physician, and to the drug itself. Risk factors for nonadherence have been identified, and include younger age, African American race, and poor overall health.

**Dr Parrish:** What do you think are the most common reasons that your patients are nonadherent to medical therapy?

**Dr Realini:** For most of our patients, the disease is diagnosed incidentally and is asymptomatic. We ask patients to take it on faith that they have a blinding disease, and our ability to convince them to take responsibility for dosing every day is directly tied to the strength of the relationship we form with them. In reality, the only symptoms most of our patients will ever experience from glaucoma are the side effects of the therapies we prescribe. Patients only get negative reinforcement. There is no positive reinforcement. There are no symptoms of glaucoma that therapy improves. The patients are left with no perceptible benefit of therapy and significant deterrents: tolerability, safety issues, cost, and the inconvenience of daily dosing. These are significant hurdles to overcome.

Both patient and physician behaviors and beliefs can contribute to nonadherence. Characteristics attributable to treatment itself can also adversely affect adherence. Qualities such as tolerability, safety, convenience of dosing, and cost can all contribute to nonadherence. To effectively assist our patients in optimizing adherence to glaucoma therapy, we must understand the reasons why adherence is suboptimal. The Glaucoma Adherence and Persistency Study (GAPS) evaluated both patient-centered and physician-centered barriers to adherence to glaucoma therapy.

**Patient Behavior**

Health-related beliefs of patients are a key determinant of adherence. In the GAPS study, several patient beliefs that were associated independently with low adherence were identified. These included not believing that reduced vision is a risk of having a problem paying for medications and not taking medication as recommended or having difficulty, especially while traveling or being away from home. Knowledge of these barriers can inform the design of better interventions to reduce nonadherence and preserve visual function among patients with POAG.

Interventions designed to address the barriers to adherence can improve patient behavior. A study of 196 patients with glaucoma who were treated with a prostaglandin analogue evaluated adherence using the Travatan Dosing Aid (TDA) (Alcon, Fort Worth, TX). In this cohort, the mean adherence rate over 3 months was 71%. Overall, only 56% of subjects took >75% of expected doses. Of note, physicians were found to be unable to identify the patients who were nonadherent. The subjects from this study who took 75% or less of their expected doses were entered into a randomized trial, in which half underwent a structured intervention designed to educate on the need for adherence, barriers to adherence, and solutions to poor adherence, and which provided regular dosing reminders by telephone; the remaining half was told to continue the drops as prescribed, with no intervention. These subjects’ adherence was again monitored for 3 months using the TDA. Those in the intervention group showed a significant improvement in adherence, from a mean of 54% to 73%, whereas the control group’s adherence remained statistically unchanged (46% to 51%). This study demonstrated that appropriate interventions can positively affect adherence.

**Tolerability/Side Effects**

Tolerability encompasses specific complaints, such as allergy, stinging, burning, blurred vision, hyperemia, and ocular surface effects. These issues provide negative feedback that diminishes the dosing incentive, which is already quite low, given that many patients with glaucoma are asymptomatic and perceive no appreciable benefit from therapy.

The topical adverse events associated with eye drop glaucoma medications can be attributable to excipient ingredients in the drug formulations, such as preservatives. The chronic use of benzalkonium chloride–preserved topical IOP-lowering therapy can contribute to ocular surface disease signs and symptoms and chronic subconjunctival inflammation.

Issues with tolerability have an effect beyond adherence. Hyperemia is a common adverse event associated with the use of prostaglandin analogues. In a prospective, 12-week, investigator-masked trial, hyperemia rates with the 3 prostaglandin analogues ranged from 47.1% (latanoprost) to 58.0% (travoprost) and 68.6% (bimatoprost). It has been shown that the extra office visits and medication switches necessitated by the occurrence of hyperemia when initiating prostaglandin therapy effectively doubles the cost of care compared with that of patients who experience no hyperemia.

**Dr Parrish:** To what extent do the topical and local side effects of IOP-lowering treatments affect adherence to therapy?

**Dr Tsai:** This varies from patient to patient. Some can tolerate significant side effects to protect their visual function, whereas others are intolerant to even the mildest conjunctival hyperemia. To some extent, the expectations and/or perceptions of patients govern the degree of this tolerability. Mild hyperemia may not be a significant issue for an older, retired patient, but can be significantly bothersome in a young executive who must function daily in professional settings.

**Dr Fechtner:** One factor that may explain intolerance to the ocular side effects of therapy is the unrecognized prevalence of ocular surface disease in our glaucoma practices. We evaluated the prevalence of ocular surface complaints in patients with glaucoma and found that 50% of the patients on topical IOP-lowering therapy reported some degree of ocular surface discomfort, of whom more than half fell into the moderate or severe range (Figure 2).

---

**Figure 2.** Prevalence of mild, moderate, and severe symptoms of ocular surface disease in treated patients with glaucoma. Numbers in parentheses represent Ocular Surface Disease Index scores.

Dr Parrish: Your excellent study and others have contributed to a
genereal recognition that ocular surface disease is far more common
among our patients than we realized.22 Patients with inflamed
meibomian glands and loss of glandular structure are those who are
more likely to tell me that their eyes are irritated and uncomfortable.

Dr Fechtner: The addition of a second drug increases symptoms of
ocular surface disease.21 Both the active ingredient and the excipients
(including the preservative) can be implicated. Patients without ocular
surface disease may have the ability to tolerate a nominal preservative
load. In 1 study, patients on no medications or 1 preserved medication
had a similar ocular surface status, but when a second preserved
medication was added, there was a substantial increase in ocular
surface symptoms.22 For our patients with preexisting ocular surface
disease, this ability to tolerate preservatives may be reduced or lost, and
they can become symptomatic with a single medication.

**Physical Limitations**

Dr Parrish: In addition to tolerability and side effects, what are some
other reasons for therapeutic nonadherence to glaucoma treatment?

Dr Fechtner: A number of physical limitations can contribute to
nonadherence. These include issues such as tremor or arthritis,
which prevent self-dosing of topical eye drop medications. There
are also cognitive issues, such as memory loss or dementia, which
preclude reliable self-care.

Dr Realini: In these patients, I often try to enlist a spouse or
caregiver to assist with dosing. In some cases, medical therapy
becomes impractical, and I find that laser trabeculoplasty is a
useful alternative in this clinical setting. There is 1 other form of
nonadherence worth mentioning. We all have patients who run out
of their medication before the end of the month and cannot get refills
until the calendar runs out. A few days of nonadherence at the end
of every month can add up to significant progression over time, and
this is in patients who are making every effort to be adherent.

**Physician Behaviors**

Physician behaviors also play an important role in patient adherence.
The GAPS research team evaluated physician beliefs and behaviors
related to adherence.11 The investigators found that physicians generally
fell into 3 categories. The first were “reactives,” who tended to avoid
considering the extent or causes of nonadherence unless compelled
to react if patients raised the issues. The second were “skeptics,” who
acknowledged the problem of nonadherence, but had little faith that
they could change patient behaviors, so they did not generally discuss
nonadherence with patients. The third were “idealists,” who recognized
the problem, believed they could help make it better, and actively
addressed adherence with their patients. Interestingly, the idealists
were also more likely to engage in active patient education, reinforcing
key messages about the risk of blindness, the need for adherence, and
techniques for medication dosing.

**NONADHERENCE AND RISK OF GLAUCOMA PROGRESSION**

The frequency with which a medication is dosed—once, twice,
or 3 times daily—is determined by its duration of action. Dosing
medications less frequently than indicated creates gaps in therapy,
during which IOP can rise and cause optic nerve damage. It therefore
stands to reason that frequently missing doses can lead to inadequate
treatment of glaucoma, which can contribute to disease progression
over time.

Several studies have evaluated the effect of nonadherence on
glaucoma progression, with mixed results. One study from the
era of pilocarpine evaluated a medicine dispenser—designed by
the investigators—that recorded the date and hour that the bottle
was opened.24 In this study, the extent of adherence to therapy was
not found to be a predictor of glaucoma progression, but the type
of glaucoma, severity of visual field defects, and mean IOP were
significant predictors of progression.

A study in 1993 evaluated 72 patients followed for 5 years to identify
factors associated with progressive glaucomatous optic neuropathy.25
Patients in this study who lost visual function were significantly more
noncompliant with medical or surgical recommendations for treatment
than those whose vision remained stable (P < .001). Glaucoma
progressed in 50% of all patients noted to have poor compliance,
whereas glaucoma remained stable in 90% of compliant patients.

In the modern drug era, a study in 2011 evaluated the relationship
between adherence and progression in 35 patients with glaucoma
administering travoprost or travoprost/timolol using the TDA for
36 months.26 The mean adherence rates were 72% after 1 month
of follow-up and 77% at 12 months. Overall, 71.4% of the patients
maintained stable visual fields and had a median adherence rate
of 85%. The remaining 28.6% of patients experienced visual field
progression during the study and had a median adherence rate
of 21% (P < .001). Patients with an adherence rate of at least 90%
remained stable, whereas 43.5% of the patients with an adherence
rate below 90% progressed (P = .01) (Table 1).

Table 1. Relationship Between Adherence and Progression in Glaucoma*26

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Worsened Visual Field (n = 10)</th>
<th>Stable Visual Field (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 (67-73)</td>
<td>69 (61-74)</td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>2 (0.75-4)</td>
<td>2 (1.5)</td>
<td></td>
<td>.72</td>
</tr>
<tr>
<td>45% (20%-45%)</td>
<td>88% (75%-97%)</td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>0 (0%)</td>
<td>12 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (14.3%)</td>
<td>12 (85.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (88.9%)</td>
<td>1 (11.1%)</td>
<td></td>
<td>&lt;.001†</td>
</tr>
</tbody>
</table>

Data are median (interquartile range)

† Mann-Whitney

‡ Test for trend

Dr Parrish: What is the strength of evidence linking poor adherence
with medical therapy and the risk of glaucoma progression?

Dr Realini: We lack the tools and methods for measuring adherence.
The patients who consent to participate in an adherence study
may represent a biased sample of those most likely to be adherent.
Also, knowing that they are being monitored likely motivates better
adherence. Therefore, estimates of adherence may be inflated. We
cannot easily obtain objective assessments of adherence.

Dr T sai: Very few studies have directly addressed this important
question. Logically, we all believe poor adherence contributes to
inadequate IOP control and ultimately results in disease progression.

**STRATEGIES FOR BETTER ADHERENCE**

Dr Parrish: What can we do to help our patients become more
adherent to medical therapy?
Dr Parrish: How do we ask our patients about adherence?

Dr Tsai: Using open-ended questions is better than simply asking, “Are you taking your medications regularly?” Also, as a rule of thumb, if a patient admits to some degree of nonadherence, the severity of the issue is likely worse than what is admitted.35

Dr Realini: I go 1 step further when I talk to my patients about adherence. I say, “We all miss a dose of our medicine every now and then. Roughly how many times a week or every 2 weeks do you think you miss a drop?” This grants them permission right up front to be honest with you. I get what I think is a more honest answer. I agree with Dr Tsai that if patients admit to missing 1 or 2 doses, it is probably twice that or more.

Dr Fechtner: Because adherence and tolerability are linked, it is important to discuss potential side effects at the time we are prescribing a new therapy. This gives patients a chance to decline a drug with unacceptable side effects. It also prepares patients for what they may experience once they start the medication. I believe patients can best tolerate adverse effects if you discuss them in advance.

Dr Tsai: Using an electronic medical record has made me aware that focusing on adherence to 1, 2, or even 3 glaucoma medications is only a small part of the bigger picture. Our patients are on many systemic medications for other medical conditions. For these patients, therapeutic adherence is a bigger issue than can be addressed in our office.

Dr Parrish: This is an excellent observation. As we face an aging population, the burden of eye drops cannot be considered just as an ocular burden, but one on their general medical health because the patients are taking so many medications already.

Dr Tsai: Also, every additional drop we prescribe will negatively affect adherence to the currently prescribed medication.28

Dr Realini: When we advance therapy, our patients may retreat from it. “Using open-ended questions is better than simply asking, ‘Are you taking your medications regularly?’” – Dr Tsai

“I believe patients can best tolerate adverse effects if you discuss them in advance.” – Dr Fechtner

Counseling for Better Administration and Adherence

Discuss potential adverse effects of medications at the time you prescribe them.

Engage the patient by saying, “Tell me how you are taking your medications,” rather than asking questions that can be answered “Yes” or “No.”

Acknowledge that we all periodically miss a dose. Ask the patient, “Roughly how many times a week or every 2 weeks do you think you miss a drop?”

EMERGING THERAPIES FOR BETTER TOLERABILITY

After a 20-year gap in glaucoma drug innovation, several novel IOP-lowering compounds are in development, potentially offering new ways to lower IOP.

Latanoprostene Bunod

Latanoprostene bunod (LBN) is a modification of the latanoprost molecule that adds a nitric oxide–donating moiety to the compound. Latanoprostene bunod offers a dual mechanism of action: the latanoprost component increases aqueous outflow through theuveoscleral pathway, and the nitric oxide component activates the cyclic guanosine monophosphate pathway, leading to trabecular relaxation and increased conventional outflow.29 A phase 2 study showed LBN provided superior IOP reduction compared with latanoprost (by 1-1.5 mm Hg; P ≤ .009).30 In this study, the conjunctival/ocular hyperemia rate was comparable in the combined LBN-treated groups (7%) and in the latanoprost group (8.5%). In a pair of phase 3 studies, compared with timolol, 0.5%, dosed twice daily, once-daily dosing of LBN, 0.024%, produced a lower mean IOP at each of the 9 time points (8 AM, 12 PM, and 4 PM at weeks 2, 6, and 12) in 1 study,31 and at 8 of 9 time points in a second study.32 Common side effects (> 2% incidence) included eye irritation (3.9% vs 2.2% for timolol) and conjunctival hyperemia (2.8% vs 1.5% for timolol).31

Rho-Kinase Inhibitors

The Rho-kinase inhibitor netarsudil mesylate also lowers IOP through several distinct mechanisms. The molecule inhibits the enzyme Rho kinase, which results in trabecular relaxation and produces IOP reduction via increased trabecular outflow and reduced episcleral venous pressure.33,34 This drug also inhibits the norepinephrine transporter, which increases adrenergic activity, reducing aqueous production. Two phase 3 trials have been completed, but have not yet been published. Development of this drug includes both a single agent and a fixed combination with latanoprost. In a phase 2b, 28-day study evaluating the fixed combination compared with either agent dosed separately, mean IOP reduction of the fixed combination was 7.8 to 8.6 mm Hg, compared with 6.3 mm Hg for netarsudil mesylate monotherapy and 7.6 mm Hg for latanoprost monotherapy.35 The most common side effect was conjunctival hyperemia, which occurred in 40% to 41%, 40%, and 14% of patients receiving the fixed combination, netarsudil mesylate monotherapy, and latanoprost monotherapy, respectively. Fixed combinations offer a simplified regimen and a reduction in exposure to excipients.36

Adenosine Agonists

Trabodenoson is an adenosine receptor agonist with high affinity and specificity for the adenosine A1 receptor. When activated, the A1 receptor lowers IOP through several distinct mechanisms. The molecule inhibits the A1 receptor lowers IOP in nonhuman primates, in part by regulating the composition of the extracellular matrix of the trabecular meshwork, resulting in increased aqueous outflow.37,38 A topical ophthalmic formulation of trabodenoson is in clinical development for the reduction of elevated IOP in patients with ocular hypertension or POAG. In a phase 1 evaluation, the drug was well tolerated, with eye pain being the most common ocular side effect (< 10%), and demonstrated no systemic accumulation or toxicity.39 Only 1 subject experienced hyperemia. In a dose-ranging phase 1/2 study, IOP reductions with the highest tested dose ranged from -4 to -7 mm Hg.40 In this study, the prevalence of conjunctival hyperemia did not increase from pretreatment baseline in any dose group. Phase 3 clinical development is under way.41

Sponsored Supplement
Dr Parrish: What is the unmet need in glaucoma medical therapy?

Dr Realiini: We tend to focus on efficacy, but the prostaglandin analogues set the bar very high for efficacy. A new drug does not need to have better efficacy than a prostaglandin to be of value. A drug with equal efficacy to a prostaglandin, but which is better tolerated, would satisfy the unmet need of patients who cannot tolerate prostaglandin side effects.

Dr Fechtner: Likewise, a drug with similar efficacy and safety that is dosed less often than a prostaglandin would have value for many patients. One or more of the novel drug delivery systems described above may satisfy this unmet need. 

Dr Tsai: These are all promising new drugs. Their place in our treatment strategy will only become apparent once they are approved and we gain experience with them.

**SUMMARY**

The goal in managing patients with glaucoma is to optimize their quality of life as they live with the disease. Both the disease and its treatment can adversely affect quality of life. Reduction of IOP is the only established therapy for glaucoma, and therapeutic adherence remains a significant clinical challenge in maintaining target IOP. Nonadherence to therapy can lead to progression of glaucoma. The side effects of therapy—particularly ocular tolerability issues—is a common reason why patients do not take their medications regularly. Selection of therapy should consider its direct effect on quality of life in relation to its side-effect profile, as well as the indirect effects that may occur if tolerability issues lead to nonadherence and disease progression. Physicians and patients can work together to optimize therapeutic adherence. Novel drugs in development may provide new options for well-tolerated therapy.

**REFERENCES**

10. Tsai JC, McClure CA, Ramos SE, Schlichting DG, Pichert JW. Compliance barriers in glaucoma: side effects of therapy—particularly ocular tolerability issues—is a common reason why patients do not take their medications regularly. Selection of therapy should consider its direct effect on quality of life in relation to its side-effect profile, as well as the indirect effects that may occur if tolerability issues lead to nonadherence and disease progression. Physicians and patients can work together to optimize therapeutic adherence. Novel drugs in development may provide new options for well-tolerated therapy.

**VISIT:** http://tinyurl.com/glaucomatherapy for online testing and instant CME certificate.
CME POST TEST QUESTIONS

1. Which of the following would not raise your estimate of a patient’s risk for glaucoma progression?
   a. Disc hemorrhage
   b. Thin central cornea
   c. Hyperopia
   d. Older age

2. Regarding adherence with glaucoma therapy, it is true that:
   a. Nearly 80% of patients take their glaucoma medications regularly
   b. Physicians can easily identify nonadherent patients
   c. It is not possible to improve patients’ adherence to glaucoma therapy
   d. Nonadherence can involve both not taking medications and not keeping appointments

3. Risk factors for nonadherence include:
   a. Younger age and Hispanic ethnicity
   b. African American race and older age
   c. Younger age and poor overall health
   d. Myopia and diabetes

4. Conjunctival hyperemia occurs in ___________ patients using topical prostaglandin analogues.
   a. 8% to 17%
   b. 14% to 22%
   c. 33% to 45%
   d. 47% to 69%

5. What percentage of treated patients with glaucoma have symptoms of ocular surface disease?
   a. 10%
   b. 25%
   c. 50%
   d. 75%

6. Which of the following is a potential consequence of adding a second medication to a patient whose glaucoma is inadequately controlled on a single medication?
   a. The risk of ocular surface symptoms increases
   b. Adherence to the first medication improves
   c. Patient experiences improved quality of life
   d. The visual field test improves

7. Physicians can address adherence by:
   a. Asking patients, “Do you take your drops every day as prescribed?”
   b. Recognizing that many patients are nonadherent to therapy
   c. Assuming they can identify the nonadherent patients in their practice
   d. Minimizing the risk of side effects when initiating new therapy

8. Which of the following is the correct pairing of an IOP-lowering drug and its mechanism of action?
   a. Latanoprostene bunod increases both trabecular and aqueous production
   b. Trabodenoson increases trabecular outflow
   c. Netarsudil mesylate increases trabecular outflow and episcleral venous pressure
   d. Latanoprost increases aqueous production

For instant processing, complete the CME Post Test online http://tinyurl.com/glaucomatherapy

To obtain AMA PRA Category 1 Credit™ for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test at http://tinyurl.com/glaucomatherapy. See detailed instructions under To Obtain AMA PRA Category 1 Credit™ on page 1.
Glaucoma Medical Therapy: Ocular Tolerability, Adherence, and Patient Outcomes

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. Mail or Fax this completed page to New York Eye and Ear Infirmary of Mount Sinai—ICME, 485 Madison Avenue, 17th Floor, New York, NY 10022 (Fax: 212-353-5703). 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 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.

PARTICIPANT INFORMATION
(Please Print)  Home  Office

Last Name ___________________________ First Name ___________________________
Specialty ___________________________ Degree  MD  DO  OD  PharmD  RPh  NP  RN  PA  Other ___________________________
Institution ___________________________
Street Address ___________________________
City ___________________________ State __________ ZIP Code ___________________________ Country ___________________________
E-mail ___________________________ Phone ___________________________ Fax ___________________________

Please note: We do not sell or share e-mail addresses. They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.

Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, New York Eye and Ear Infirmary of Mount Sinai Institute for CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. CME certificates cannot be awarded unless you answer this question. For additional information, please call NYEE ICME at 212-979-4383. Thank you.

☐ Yes  ☐ No  I and/or my family member have a financial relationship with New York Eye and Ear Infirmary of Mount Sinai and/or refer Medicare/Medicaid patients to it.

☐ I certify that I have participated in the entire activity and claim 1.0 AMA PRA Category 1 Credit™.

Signature Required ___________________________ Date Completed __________

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:

• Counsel patients on optimal administration and adherence strategies  5  4  3  2  1
• Describe the effect of tolerability of glaucoma medications on patient adherence  5  4  3  2  1
• Describe the mechanism of action of current and emerging topical glaucoma therapies  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. 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

5. 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