



Glaucoma Today

MODERN OPTOMETRY

GLAUCOMA TREATMENTS IN 2021:

Personalizing Patient Needs

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Glaucoma Treatments in 2021: Personalizing Patient Needs

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CONTENT SOURCE

This continuing medical education (CE/CME) activity captures content from a roundtable in August.

ACTIVITY DESCRIPTION

Based on a roundtable held in August, this supplement summarizes a discussion of the mechanisms of actions and challenges with currently available and novel therapeutics as well as how to personalize glaucoma treatments.

TARGET AUDIENCE

This certified CME/CE activity is designed eye care providers involved in the management of glaucoma and associated disorders.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Describe** the mechanisms of action of novel therapeutics and classes of drugs for ocular hypertension (OHT) and primary open-angle glaucoma (POAG)
- **Interpret** the challenges and limitations associated with currently available pharmacologic treatment options for OHT and POAG
- **Evaluate** monotherapy and combination regimens and **compare** which option is most likely to achieve each individual patient's goal IOP
- **Compare and assess** the efficacy of novel therapeutics with traditional prostaglandins

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PRETEST QUESTIONS

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY EVALUATION/ SATISFACTION MEASURES FOR CE/CME CREDIT.

1. Please rate your confidence in your ability to apply updates in personalizing glaucoma treatment in the clinic. (Based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident.)
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
2. Sustained-release glaucoma treatments are likely to help which group of patients the most?
 - a. Patients with ocular surface disease who are struggling with drop adherence
 - b. Patients on maximum medical therapy
 - c. Patients with advanced glaucoma who need significant IOP reduction
 - d. Patients with early stage glaucoma who need moderate IOP reduction
3. Which of the following nitric oxide-donating moieties improves trabecular outflow?
 - a. Netarsudil
 - b. Netarsudil and latanoprost
 - c. Latanoprostene bunod
 - d. Selective laser trabeculoplasty (SLT)
4. Which of the following is true about the relationship with corneal hysteresis and risk of glaucoma?
 - a. Lower corneal hysteresis is associated with an increased risk of glaucoma
 - b. Lower corneal hysteresis is associated with a decreased risk of glaucoma
 - c. Corneal hysteresis is not associated with glaucoma
 - d. Corneal hysteresis is the main predictor of propensity to glaucoma
5. A _____ reduction in IOP is necessary to reduce the risk of progression according to the Collaborative Normal Tension Glaucoma Study.
 - a. 5%
 - b. 20%
 - c. 30%
 - d. 40%
6. According to the real-world MOST study, what percentage of patients will experience hyperemia on ROCK inhibitors?
 - a. 5%
 - b. 20%
 - c. 30%
 - d. 40%
7. Which IOP-lowering therapy targets the uveoscleral outflow?
 - a. SLT
 - b. Minimally invasive glaucoma surgery (MIGS)
 - c. Prostaglandin analogs (PGAs)
 - d. ROCK inhibitors
 - e. None of the above
8. Which of the following statements about patient compliance and dosing is TRUE?
 - a. Compliance decreases with decreased dosage regimen and complexity
 - b. Compliance increases with decreased dosage regimen and complexity
 - c. Less frequent dosing results in worse compliance
 - d. There is more compliance with QID drop regimens than with QD drop regimens
9. When counseling patients on the potential side effects of ROCK inhibitors, which of the following talking points should be made?
 - a. Hyperemia is common, is not an allergy, and may improve with time
 - b. Any hyperemia is due to an allergy to the medication, and they will need to discontinue use
 - c. Systemic side effects are a concern, and you should not use it if you're pregnant or thinking of becoming pregnant
 - d. Verticillata is a potential concern and may impact their vision
10. You are seeing a 53-year-old woman who presents for routine exam. You note high IOP at 28 mm Hg in both eyes. She has an enlarged cup-to-disc ratio in both eyes as well as a family history of glaucoma. She desires therapy with a drop, and she wants to minimize her dosing schedule. Which of the following is a first-line agent for this patient?
 - a. Carbonic anhydrase inhibitor
 - b. PGAs
 - c. Latanoprostene bunod
 - d. Alpha-adrenergic agonists
11. All of the following are mechanism of actions of netarsudil EXCEPT:
 - a. Increased aqueous humor production
 - b. Increased trabecular outflow
 - c. Decreased episcleral venous pressure
 - d. Decreased trabecular outflow
12. Sonia, a 50-year-old newscaster, presents for a routine exam, complaining of blurry vision. Her IOP is 26 mm Hg in her right eye and 24 mm Hg in her left. She has no family history of glaucoma and normal central corneal thickness. Her OCT is unremarkable, but her visual field reveals an inferior defect on the macular cube on her right eye. She's diagnosed with glaucoma, with a target pressure in the low teens. Her job is unpredictable, causing her to work odd hours, and she is frequently on camera. What first-line treatment might be most appropriate for Sonia?
 - a. Latanoprostene bunod
 - b. Latanoprost
 - c. OMNI
 - d. SLT
13. Dan is a 65-year-old man with diabetes, hypertension, and moderate glaucoma. He is on combination netarsudil and latanoprost for IOP control with mixed success. He is not always adherent to therapy, causing his pressures to range from 8 mm Hg to 17 mm Hg. He presents complaining of reduced visual acuity, which is due to a visually significant cataract. His current pressures are 19 mm Hg in both eyes. What is the next treatment step for this patient?
 - a. Cataract extraction, IOL implantation, and MIGS
 - b. SLT
 - c. Sustained-release bimatoprost
 - d. Trabeculectomy

Glaucoma Treatments in 2021: Personalizing Patient Needs

For the nearly 3 million Americans with primary open-angle glaucoma (POAG), medical therapy is the first-line choice to lower IOP. However, these agents have several limitations and barriers that can include compliance, tolerability, and effectiveness.¹ Second- and third-line treatments for patients on maximum medical treatment are laser and surgical procedures, yet there is increasing evidence that laser treatment should have a more prominent role in the first-line setting.² Further, novel mechanisms of action are changing the pharmacologic landscape as new agents are approved.³ These new agents provide clinicians with multiple options for POAG management, allowing for a more personalized care approach. The following roundtable discussion brings together experts in glaucoma management to discuss the current treatment landscape and how to create personalized care plans to optimize the outcomes for our patients with glaucoma.

—Nathan M. Radcliffe, MD, Program Chair

THE NEED FOR A PERSONALIZED APPROACH TO GLAUCOMA MANAGEMENT

Nathan M. Radcliffe, MD: Glaucoma is a challenging disease that requires us to use all of the tools at our disposal. Being a glaucoma specialist is a journey of constant learning because we haven't yet solved this disease. Patients are still losing vision, and we know we can do better. We must continue to try to find and implement the new and best therapies.

Q | Dr. Fingeret, you're an imaging expert. What can you tell us about visual field damage and glaucoma?

Murray Fingeret, OD, FAAO: Glaucoma is often thought of as a group of progressive optic neuropathies that have in common a slow progressive degeneration of the retinal ganglion cells and their axons.⁴ This process results in a distinct appearance of the disc and a concomitant pattern of field loss. Glaucoma diagnosis is still essentially clinical; unlike glucose for diabetes, there's no marker to make the diagnosis of glaucoma.¹

The causes of glaucoma are complex. Although IOP is the mainstay of glaucoma treatment, elevated IOP is not a prerequisite for diagnosis; low levels of IOP can stress the optic nerve head of connective tissue.¹ There are other things occurring, such as blood flow, ischemia, oxidation, and aging.⁵ What separates the glaucomatous optic neuropathy from the other optic neuropathies are the specific changes that occur within the ganglion cell layer. The remaining layers of the retina are relatively intact as glaucoma occurs.⁶ But with that, there's an excavation that occurs to the optic nerve, the so-called 'bean potting.'

One of the challenges on the optometry side is that optometrists are not assessing the optic nerve like they once did. Our reliance on optical coherence tomography (OCT) has caused optometrists to pay more attention to the nerve fiber layer and the macular region. OCTs don't always do as good a job with imaging the optic nerve.⁷ The good news is there's a host of refinements that are occurring

with the OCT. Donald C. Hood, PhD, of the Hood Visual Science Lab at Columbia University, has spoken a lot about this. He was the first to actually flip the nerve fiber layer and put the temporal area in the middle, which allows better structure/function correlations so you can look at the field and nerve and assess the changes and how they correlate.⁸

Dr. Radcliffe: Dr. Fingeret, you bring up a great point about where we are with imaging. As for what causes damage to the optic nerve, there are risk factors and modifiable risk factors. There's data indicating that low cerebral spinal fluid (CSF) pressure is associated with nerve damage.⁹⁻¹² Low ocular perfusion pressure may also be associated with visual field progression.¹³

Q | Dr. Provencher, what can you tell us about elevated IOP as both a risk factor and a modifiable risk factor?

Lorraine M. Provencher, MD: Glaucoma is definitely a multifactorial disease.¹⁴ However, in 2021, we still tend to approach treatment in a unilateral fashion by lowering IOP.¹ As Dr. Radcliffe mentioned, there's exciting work being done with intracranial pressure (ICP) indicating that low CSF pressure is an independent risk factor for glaucoma.¹¹ We may one day have the ability to address ICP, but for now, lowering IOP is the main modifiable risk factor we have. Fortunately, we have great evidence to back up this approach. Multiple, large, randomized clinical trials have established the effectiveness of lowering IOP at reducing the risk of glaucoma progression and reducing the risk of conversion to glaucoma in patients with ocular hypertension.¹⁴⁻¹⁸ The Ocular Hypertension Treatment Study (OHTS) showed that treatment to lower IOP led to a reduced risk of developing glaucoma at 5 years from 9.5% to 4.5%.¹⁵ The Early Manifest Glaucoma Trial (EMGT) found that a reduction in pressure by 25% reduced the risk of progression from 60% to 45%.^{14,19,20} It also found that each pressure point matters,

which has since been backed up with other studies. Along those same lines, the Collaborative Normal Tension Glaucoma Study (CNTGS) was able to reduce progression in normal tension glaucoma patients through a 30% reduction in IOP.¹⁸

The Advanced Glaucoma Intervention Study 7 (AGIS-7) showed that in advanced glaucoma, IOP control over time results in less visual field deterioration.¹⁶ In 2015, the United Kingdom Glaucoma Treatment Study (UKGTS) compared the use of a prostaglandin analog to placebo, and found that treatment lowered IOP and preserved the visual field out to 2 years.¹⁷ All of these studies provide convincing evidence that pressure reduction makes a difference.

Jason Bacharach, MD: I'm glad you brought up EMGT, which was an interesting, population-based study with 7 to 11 years of follow-up. A total of 255 patients, aged 50 to 80 years, with early-stage glaucoma in at least one eye were randomly assigned to initial treatment with a selective beta blocker and argon laser trabeculoplasty (ALT), or left untreated until signs of progression appeared.¹⁴ There were no target pressures set; you got what you got. The reason they performed ALT was because you knew patients would get therapy, and it took compliance out of the picture. At the time, the beta blocker was one of the better treatment options available because prostaglandin analogs (PGAs) weren't yet available on the market. Patients in the treatment arm had a 25% reduction in pressure, but still had a high progression rate of 59% at 9 years.^{14,19,20} Translating this into clinical practice, when we set target pressure goals, in many cases those goals aren't low enough.

Dr. Fingeret: I look at the EMGT and UKGTS studies as bookends. EMGT showed how many patients progress and UKGTS showed how quickly they change, which can be 12 to 18 months.¹⁷ You're right, Dr. Bacharach, we should look at target pressures and how we are treating these patients.

Dr. Provencher: I agree, and it's not just target pressures, it's about custom treatment options for patients over time.

Dr. Radcliffe: EMGT showed that one size doesn't fit all and that 25% pressure reduction probably isn't sufficient, on average.¹⁴

THE CURRENT TREATMENT LANDSCAPE

Current pharmacologic therapies and novel mechanisms of action

Q | DR. RADCLIFFE: Dr. Bacharach, what is your view of the pharmacologic landscape for glaucoma treatment today?

Dr. Bacharach: For years, the emphasis was on lowering IOP, but whether you looked at pharmacologic, laser, or surgical management with minimally invasive glaucoma surgery (MIGS), a lot of emphasis has shifted to also considering mechanism of action.¹ There's really only three mechanisms of action with pharmacologic

glaucoma treatment. We can improve the trabecular or uveoscleral outflow or decrease aqueous production.

Multiple drug classes have either a primary mechanism of action or a secondary mechanism to increase the trabecular or conventional outflow. Netarsudil 0.02% was the first Rho-kinase (ROCK) inhibitor approved in the United States and second ROCK inhibitor approved in the world.²¹ PGAs have a secondary effect of lowering IOP.^{17,22} Nitric oxide-donating moieties also improve trabecular outflow. Right now, we have one available in the United States, latanoprostene bunod 0.024% linked to a PGA.²³ Pilocarpine, which is not widely used but very effective, mechanically opens the trabecular outflow pathway. There are other classes of agents in clinical trials right now that appear to demonstrate improved conventional outflow through the trabecular pathway (including omidenepag isopropyl^{24,25} and NCX-470^{26,27}).

The other bucket of outflow activity is uveoscleral outflow, which PGAs target. Since the CyPass was pulled off the market, we don't have a primary surgical mechanism of action to improve uveoscleral outflow²⁸; other MIGS devices and procedures are in clinical trials.

Finally, the third bucket is aqueous suppression. Multiple agents suppress aqueous: alpha agonists, beta blockers, and topical carbonic anhydrase inhibitors.¹ The issue with suppressing aqueous is that we know the eye relies on aqueous for natural function. Remember, Schlemm canal has blood flow but the trabecular meshwork doesn't. The trabecular meshwork and juxtacanalicular tissues get their nutrients through aqueous. In younger individuals with a longer life expectancy, we should consider the potential long-term impact of aqueous suppression.²⁹

Ultimately, lowering IOP is paramount, but I do think mechanism of action is critical.

Dr. Radcliffe: Our three newest medications, latanoprostene bunod, netarsudil, and fixed-dose combination of netarsudil and latanoprost have novel mechanisms of action.^{3,30} Latanoprostene bunod is a nitric oxide-donating prostaglandin F2-alpha analogue, and netarsudil is a ROCK inhibitor.^{21,23} ROCK inhibitors enhance trabecular outflow. The rationale for this is that the trabecular meshwork is the primary site responsible for elevated pressure in glaucoma, making it a natural target. Rho-kinase itself increases trabecular meshwork contraction and fibrosis by contracting the actin-myosin stress fibers in the extracellular matrix. ROCK inhibitors inhibit Rho-kinase's ability to link actin-myosin, thereby inhibiting the ability to form the stress fibers in the trabecular meshwork. That causes trabecular meshwork relaxation, which can even be visualized as a more relaxed, open, and visibly porous trabecular meshwork.³¹

In addition, ROCK inhibitors have been shown to decrease episcleral venous pressure by as much as 10% in healthy and glaucomatous eyes.^{32,33} With ROCK inhibitors, we can bring more fluid through the trabecular meshwork into Schlemm canal, but also increase that driving force by lowering the episcleral venous pressure and, again, bringing more fluid through the trabecular meshwork.

This begs the question, could there be a benefit to bringing more fluid through the trabecular meshwork that is more lasting? I hope future investigations look at that important topic. The mechanism is conceptually appealing because you're addressing outflow.

Nitric oxide has a few different roles and many different functions in the human body, throughout the respiratory, urogenital, cardiovascular, and cerebrovascular systems.³⁴ Nitric oxide can be added to a PGA, such as latanoprost using the bunod modification, which allows the PGA to release nitric oxide as it enters the eye.³⁵ With latanoprostene bunod, we have a drug that releases latanoprost acid and nitric oxide in the eye. That gives us the uveoscleral outflow and also the effects of nitric oxide.³ By way of background, nitric oxide is reduced in patients with open-angle glaucoma, so it makes sense that you may be treating a deficiency by replenishing nitric oxide in eyes with elevated pressure.³⁶ Although nitric oxide is a ROCK inhibitor, it has its own effect on soluble guanylyl cyclase and cyclic guanosine monophosphate (cGMP) that inhibits calcium signaling and release from the cellular stores.³⁷ This has a similar effect in terms of trabecular meshwork relaxation as was previously discussed. We now have nitric oxide working directly through cGMP and through Rho-kinase. There's evidence in animals that nitric oxide modulates episcleral venous pressure.³⁸ Although this has not been conclusively demonstrated in humans, there is some reason to be hopeful that it may have that mechanism.

Dr. Provencher: The refocus on trabecular outflow needs to be emphasized. We now have the ability to treat at the site of the pathology, ie, conventional outflow, as opposed to uveoscleral outflow or aqueous suppression. We don't fully understand what the long-term use of aqueous suppression or PGA use does to conventional outflow. Could it actually shut down what residual trabecular meshwork-based outflow our patients have? Could treating to improve trabecular outflow instead have a positive effect over time? This is an exciting concept to consider.

Dr. Radcliffe: Although we don't yet know if these new treatments are disease modifying, it makes sense that this is the tissue you'd want to go after to have some sort of self-propagating benefit. I think it's also important to mention that both netarsudil and latanoprostene bunod are once-daily dosing, which is the secret to patient adherence. With latanoprostene bunod, you're getting two mechanisms in one bottle: uveoscleral outflow and trabecular outflow. With ROCK inhibitors, you're similarly getting multiple mechanisms with episcleral venous pressure reduction as well as trabecular outflow.³ The once-daily dosing makes pharmacologic treatment manageable.

Q | Hyperemia is a well-known side effect of these agents;³⁹⁻⁴¹ how do you prepare patients for that potential side effect?

Dr. Fingeret: Hyperemia is pervasive with all of these medications. I explain to my patients that you may see some eye

redness, that it is normal, and that it may resolve after a couple of days. Hyperemia from netarsudil and latanoprostene bunod is typically mild, but in some cases, it can be significant. For those few cases, the hyperemia is not going to get much better. Then it becomes a game of managing the redness.

Dr. Bacharach: In the MERCURY studies, 58% of patients on fixed-combination netarsudil/latanoprost had hyperemia but most of it was graded as mild. The discontinuation rate was 5%.³⁹ In the MERCURY trials, subjects were washed out at baseline, and they had relatively clear eyes. If you take a drug that you know is going to dilate the episcleral venous bed, you would expect some redness particularly from a baseline of very clear eyes. To contrast, a phase 4 study, (MOST) which enrolled 261 real-world patients already on a variety of topical therapies, there was a hyperemia rate of 20%.⁴² For me, the take-home message is that we should prepare patients for the possibility of redness during induction, but they should not stop the medication if it's tolerable and mild. The hyperemia tends to wax and wane and it was rarely present at two visits in a row during the approval studies. We should encourage our patients to stay on the drug and see if they can get through that initiation period. Remember the hyperemia is not an allergy but due to the drugs effect on the episcleral venous bed.

Dr. Provencher: I tell my patients to prepare for their eyes to be very red. It is important to set this expectation. I also stress that it is normal and not an allergy. I explain that we'll bring them back in a couple of weeks to assess its effectiveness and then decide if the redness is bothersome enough to discontinue the medication. The vast majority of patients do just fine and don't mind the mild hyperemia, especially when they see the drug is working.

Dr. Radcliffe: Setting expectations is a great approach, and I agree that many patients think the redness is an acceptable trade-off for keeping their vision. Patient perception varies. Some patients are very red and they don't perceive it as that bad; other patients are only mildly red and they think it's extreme. We don't want to assume the patient is unhappy and then plant that seed in their mind. I try to be mindful not to have my perception negatively impact their care because I want every patient who can be helped by these drugs to have their chance. It's important to find a way through the hyperemia when the patient's vision is on the line.

Selective laser trabeculoplasty as a first-line treatment

Dr. Radcliffe: The European LiGHT trial randomly assigned 718 treatment-naïve patients with open-angle glaucoma to initial selective laser trabeculoplasty (SLT; n = 356) or medical therapy (n = 362).² The trial was designed to establish if SLT is a superior first-line treatment compared with medical management. Target IOP was set based on disease severity. The primary outcome was health-related quality of life at 3 years. Secondary outcomes were

cost-effectiveness, disease-specific health-related quality of life, effectiveness, and safety. At 36 months, no significant difference in quality of life was seen between the two groups (difference, 0.012; 95% CI -0.007 - 0.031; $P = .23$). However, more patients in the SLT group maintained target IOP and avoided glaucoma surgery compared with the medical management group. Disease also progressed in a lower proportion of patients in the SLT group compared with the medical management group.

Q | SLT is becoming a first-line treatment for glaucoma. Where does SLT fit in your practice?

Dr. Provencher: I offer first-line SLT to patients with ocular hypertension, POAG, or secondary open-angle glaucomas. I present it to them as an equal option to medication. I'll use SLT anywhere in the treatment algorithm, but the results from the LiGHT trial moved SLT further up in my algorithm. The LiGHT trial showed us that, not only is SLT effective from a pressure reduction standpoint, but it is very safe and can improve adherence issues, which are a huge hurdle in glaucoma care.^{43,44}

The Travatan Dosing Aid Study found that even when patients knew they were being monitored electronically and provided free medication, 45% of patients used their drops less than 75% of the time.⁴³ Once daily dosing helps, but there are still significant adherence barriers even with the reduced drop burden.⁴⁵ SLT patients also get better day-to-day and diurnal control.

I'll also add that it is critical to learn how to present and explain SLT to patients so they are not turned off by the sound of laser. I explain that SLT is not a cure and ongoing follow-up will be needed. My SLT patients are typically very happy they chose laser, and they still continue to follow-up, even off of medications.

Dr. Radcliffe: That's such a great myth to dispel. Most doctors would select SLT for themselves if they had glaucoma, but we still struggle with ways to present it to our patients as a first-line option. We all have patients who are on drops and don't come back. Adherence is a problem whether someone has had laser or not. At least with laser, I've given them the best chance of saving their sight if they fall off therapy.

Dr. Bacharach: Most clinical studies comparing SLT to medication have found that SLT is as efficacious as our best medicines.^{46,47} The LiGHT study was conducted in England and demonstrated a cross-benefit with first-line SLT.² That was an important demonstrable endpoint. I present SLT as a first-line option to my patients, but I don't push it. Many people will choose SLT as a second option if they don't do well with drops. You can use SLT anywhere along the algorithm, but I've found it tends to work better the earlier you use it and there is good efficacy after the second treatment as well.⁴⁸ SLT is an excellent option for many patients.

Dr. Radcliffe: I've finally come to totally embrace SLT in my practice. I use it the most in the first- and second-line settings

because, as Dr. Bacharach mentioned, it works better the earlier you use it. That has also reinforced my thinking that trabecular meshwork agents should be used early on as well. If laser is most efficacious before the disease has progressed to the distal outflow pathway, then perhaps pharmacologically treating patients with outflow agents earlier could have a similar benefit.

Dr. Bacharach: That is an interesting point. Moser et al showed that success with an SLT might predict how well some of these new outflow agents might work.⁴⁹⁻⁵² I think they play on each other in terms of mechanism of action.

Dr. Fingeret: I'd like to present a different view of SLT. My experience has been that SLT does not provide the extent of IOP reduction that we get with some of the newer medications. To me, SLT is clearly an initial modality, but we must carefully monitor the patient and intervene if we start to see IOP creep up.

Minimally invasive glaucoma surgery (MIGS)

Dr. Radcliffe: In the past decade, MIGS procedures have emerged as a surgical alternative to traditional glaucoma surgery. MIGS includes a group of ab interno procedures that have a better safety profile than filtration surgery because they spare the conjunctiva and have fewer complications.^{53,54}

Q | What is your approach to MIGS in 2021? Where is MIGS headed?

Dr. Provencher: The recurring theme from this discussion is personalized care. But a second common theme is addressing traditional outflow sooner rather than later. We know MIGS are safe and minimally disruptive. They should be performed ab interno, and they are easy for the physician to perform and recovery is generally easier for patients. For these reasons, I think MIGS can be offered, with confidence, earlier in the treatment algorithm. I always consider MIGS when the patient has a visually significant cataract and needs cataract surgery. It's a great opportunity to improve IOP and reduce medications. I will also consider MIGS as a standalone option when a patient is uncontrolled on medications with a MIGS-range IOP target, intolerant to medications, or has poor adherence. For standalone cases, I typically perform a 180° goniotomy or use the OMNI Surgical System, which allows for combined ab interno trabeculotomy and transluminal viscoelastic delivery for up to 360°. This device targets multiple points of aqueous humor outflow resistance: the trabecular meshwork, Schlemm canal, and distal collector channels.⁵⁵⁻⁵⁷ MIGS is another opportunity for us to delay invasive procedures. We're detecting glaucoma earlier and treating it earlier. We're also trying to focus on things like quality of life, and I think MIGS fits perfectly with that ethos by reducing the treatment burden for the patient.

Dr. Radcliffe: Recently, I had a patient who could tolerate almost no drops, but I was still uncomfortable offering MIGS. Are we at

the point where we consider MIGS by themselves to be acceptable options for people who are sensitive to topical agents?

Dr. Bacharach: MIGS have been an incredible advance in surgical treatment for glaucoma patients. It's revolutionized my surgical treatment options to offer patients. When I look at my surgeries, eight out of 10 cataract surgeries will have some type of MIGS associated with it. As for freestanding MIGS, Sight Sciences, the manufacturer of the OMNI, has just received on-label approval for the procedure itself, goniotomy and viscocanalostomy, without cataract.^{56,58} Others are in the pipeline. For example, Glaukos has recently submitted a supplemental premarket approval application for iStent infinite. Hopefully, we'll soon have a multitude of options of freestanding MIGS, and we'll gain more clinical experience.

Dr. Radcliffe: I agree. It's challenging and probably not as simple as doing standalone MIGS all the time. It's different to get patients into the operating room for something that won't improve their vision like cataract surgery.

Novel drug-delivery systems

Dr. Radcliffe: In light of our recognition of the challenges of topical therapy, including adherence with once-daily drops,⁴⁵ the field of sustained delivery promises to offer agents typically placed inside of the eye that can lower the pressure without the use of topical agents for months or even years.

Recently, the US Food and Drug Administration approved sustained-release bimatoprost as a single injection.^{59,60} Bimatoprost can lower IOP for a period of time between 4 months to 2 years after one administration.⁶¹ My clinical experience with bimatoprost sustained release has been outstanding. Although these delivery systems require more discussion with the patient and consideration of corneal status and anterior chamber narrowing, the therapy has provided tremendous value to my patients struggling with adherence due to ocular surface disease.

The travoprost intraocular implant is in the pipeline.^{62,63} Sustained-release travoprost promises an even longer duration of action with a drug-eluting implant placed in the anterior chamber drainage angle in a minor surgical procedure. It's exciting to see that we have an out-of-the-box solution to use. I've even referred to sustained delivery in glaucoma as the fourth pillar of glaucoma care, sitting alongside topical drops, laser, and incisional surgery.

Dr. Provencher: I agree with Dr. Radcliffe. Sustained drug delivery provides a nice option

for patients who are poorly tolerant, poorly adherent to medications, or patients who desire independence from topical medications. In my experience, the bimatoprost implantation is simple for the clinician and well-tolerated by patients. I look forward to the expansion of this "fourth pillar," particularly longer-term options and delivery of additional drug classes.

Dr. Bacharach: I also agree with Dr. Radcliffe. Sustained-release drug delivery has already become an important consideration in treatment options for patients. The successful implementation of bimatoprost in our clinical practice has been very exciting. Sustained-release drug delivery is poised to create a paradigm shift in glaucoma management.

Dr. Fingeret: Drug delivery systems will become an important part of glaucoma care, the question is when. One issue is that the current techniques are invasive with significant expense and potential complications. Noninvasive delivery devices, such as contact lenses or the ring when they become available (and that is a big question) will allow optometry to this provide this method of care.

CASE 1: THE DANGERS OF UNDERTREATING "GREEN DISEASE" IN A YOUNG PATIENT

Dr. Bacharach: Our first case is a 56-year-old white woman with mildly asymmetric cupping that is worse in the right eye than left. Her mother had glaucoma and past medical history is noncontributory. She's on no systemic medicines. She's a long-time triathlete and in excellent physical condition. Her VA is 20/20 OU, and her slit-lamp exam was within normal limits. Her tonometry was 26 OU at 8 AM and 19 OU at 4 PM. Her pachymetry readings were 540 and 535. Figure 1 shows her imaging. You can see the optic nerve cupping and a Drance hemorrhage OD. Figure 2 shows her OCT evaluation, which was essentially normal in terms of the temporal-superior-nasal-inferior-temporal (TSNIT) and ganglion cell complex, although if you look closely, you can see there is actually some intra-eye asymmetry. Although it was still in the green level in most of the parameters, the TSNIT did demonstrate some

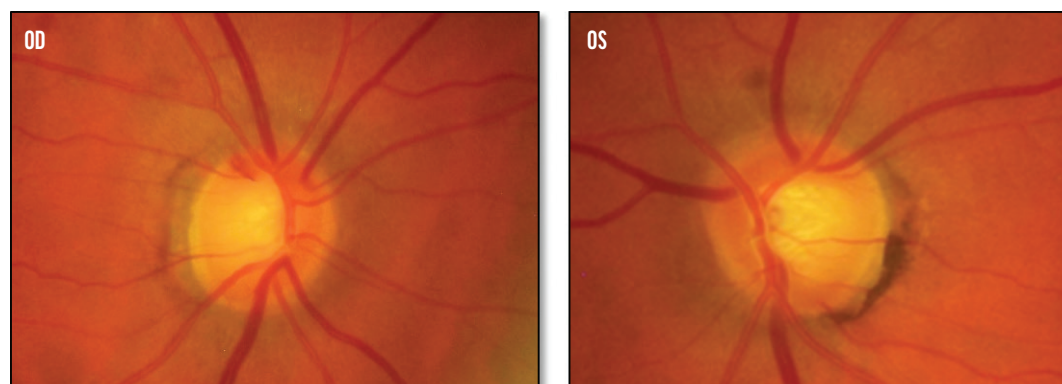


Figure 1. The patient's baseline imaging.

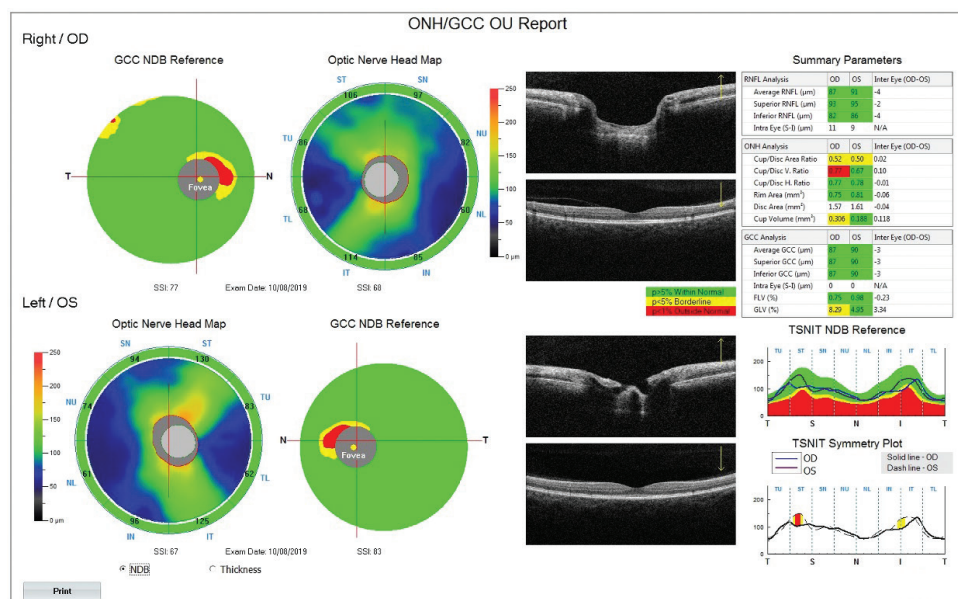


Figure 2. The patient's baseline OCT results.

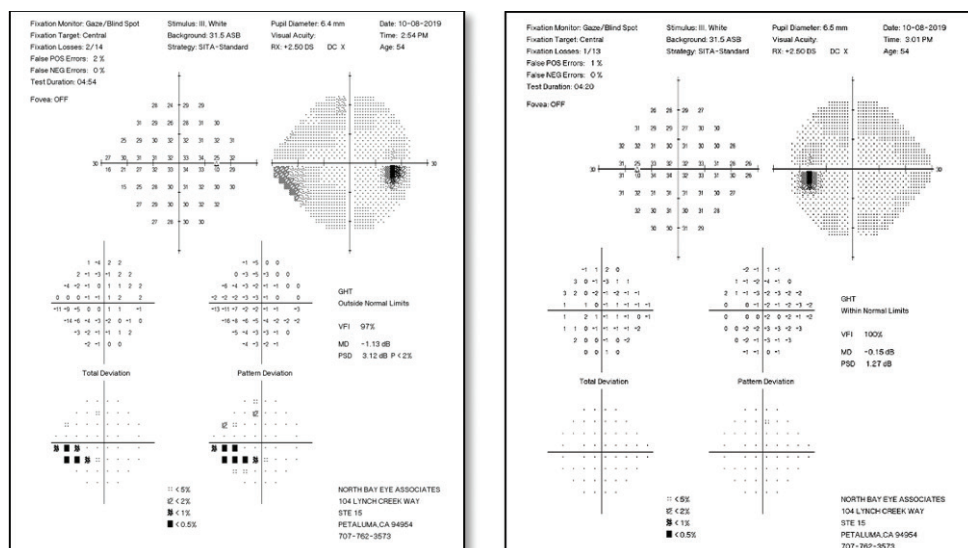


Figure 3. The patient's baseline visual field imaging.

thinning of the superior nerve in the right eye. I would call this 'green disease' in the right eye. She had a concomitant visual field defect in the right eye and inferior hemiquadrant (Figure 3).

Dr. Fingeret: The asymmetry in the right eye is clear when compared to the left. That's a big drop. It looks like it may be a little greater superiorly. It is significant in that you can see the area on the symmetry plot that it is flagged in that so-called red zone. I can't quite make out the average retinal nerve fiber layer (RNFL), but this field defect is almost classic partial arcuate scotoma inferiorly that correlates with that. That tells you how deep the RNFL drop-out is. Typically, we don't see field defects that deep until the RNFL is close to being in the 70s. What's interesting is

that you also see a superior change in the ganglion cell area that is extending almost onto the nasal side. To me, this is no longer a mild defect. We're getting into moderate defects because of the fairly significant field defect that would force a low target pressure.

Dr. Radcliffe: We tend to understage glaucoma. We tend to see a visual field defect like this and assume early glaucoma, but this is at least moderate disease. I bet if you look a little closer, you could find a defect within 10° fixation and classify it as severe. The point is we need to be aggressive in treating these cases. If we aren't careful with our staging, we may mistake this for early disease.

Dr. Fingeret: The field defect is ominous. There's probably central loss and a case that requires more than simply a first-level PGA.

Dr. Provencher: That's a great catch on an OCT and a lesson in and of itself. In a way, green disease is worse than red disease. You don't want to miss early glaucoma, and it's almost better to overtreat red than undertreat green. We must know how to read an OCT. I agree that this case is scary. This patient is young. I'd check the gonioscopy to ensure her angles are open given the degree of disease at this young age. I'm glad you have a morning IOP check and an afternoon IOP check. If you had only seen her in the afternoon when her pressures were 19 mm Hg, there wasn't a disc

hemorrhage, and her OCT looked pretty normal at quick glance, one could easily miss the diagnosis without a visual field.

I would target my treatment to lower IOP and minimize the fluctuation she's having throughout the day. Given that she's physically fit, she may have a low blood pressure (BP) at baseline and, despite likely great cardiovascular output, I'd still worry that her BP dips low. I'd like to put her on something that flattens diurnal fluctuation and is nighttime friendly. I'd probably offer a PGA or SLT. As for her target pressure, I want to reduce her IOP by at least 30%, putting her target pressure in the mid-teens. You might be able to get there with a PGA or SLT alone, but something that reduces episcleral venous pressure or improves trabecular outflow would be nice to add.

Dr. Radcliffe: We want to get to know this patient and individualize the therapy. I want to talk to her and assess her expectations. That can help guide your therapy choice, whether it's SLT, netarsudil, or latanoprostene bunod. It is nice that we have various options to capture different elements of the efficacy and risk-tolerability profile of the patient.

Dr. Provencher: If you're thinking between something like a PGA or a ROCK inhibitor, both have different cosmetic side-effect profiles.⁶⁴ For a 56-year-old woman who might be on this for a long time, a PGA may not be the best option for her cosmetically. We need to get to know her and determine if a little hyperemia might be more desirable long-term than say periorbitopathy,⁶⁵ for example.

Dr. Bacharach: On the diagnostic side, we should consider the OCT as another tool, not the be all, end all. On the therapeutic side, we should individualize treatment to a particular patient's needs and desires. This patient happens to be in the public eye, so cosmetic side effects are important, but she was willing and understood the gravity of the situation. Her mom has glaucoma and has been taking drops successfully for many years. This patient also wanted to try a drop first rather than SLT. I started a trial of latanoprostene bunod as an initial treatment. She did very well. The pressure dropped into the 16 mm Hg range, which was my initial target goal. Obviously, that's an adjustable number. Maybe it's not enough; maybe she'll need more, but for now we continue to manage her on monotherapy.

CASE 2: GLAUCOMA MANAGEMENT IN A YOUNG PATIENT WITH DIABETES

Dr. Fingeret: Our second case is a 54-year-old black man with diabetes who presented for a comprehensive eye exam. He is on metformin for HbA1c control, and his HbA1c is 8.3%. He has high blood pressure and elevated cholesterol. His last eye exam was 9 years ago, which was negative for glaucoma. His pressure at this exam is 19 mm Hg in each eye, with a corneal thickness of 536 and 528. Figure 4 shows his optic nerve in his right and left eyes. You can see several RNFL defects, both superior and inferior. The red tissue also looks extremely suspicious.

When you look at the top corner of the left eye on the RNFL thickness map (Figure 5), you can see the areas of blue that show the nerve fiber layer defects. Although they don't show up in the deviation map or in either of the quadrants or clock hours, we do see it. That's a very good way to see defects right in that thickness map. On the other side of the right eye, the defects show up even more. Because they're denser, they're also

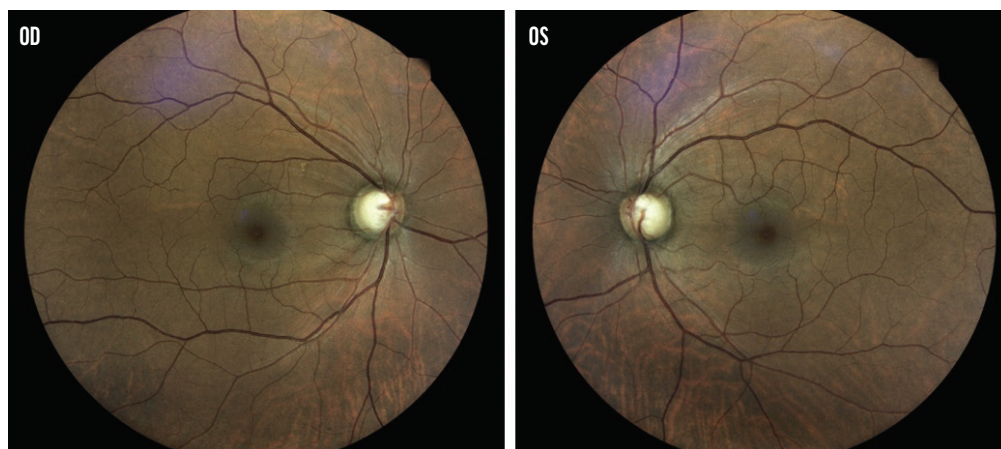


Figure 4. The patient's baseline imaging.

showing up on the deviation map as well as the quadrant and the clock hour.

Figure 6 shows the combined ganglion cell analysis and RNFL deviation map for both eyes. I like to use this because it combines the macula and the nerve fiber layer so you get an idea of the gestalt of how most defects are a continuum. Figure 7 shows the visual field results from both eyes. This person clearly has POAG, with the right eye having more disease than the left. This person is young, and the field defect is nearing the central area. There

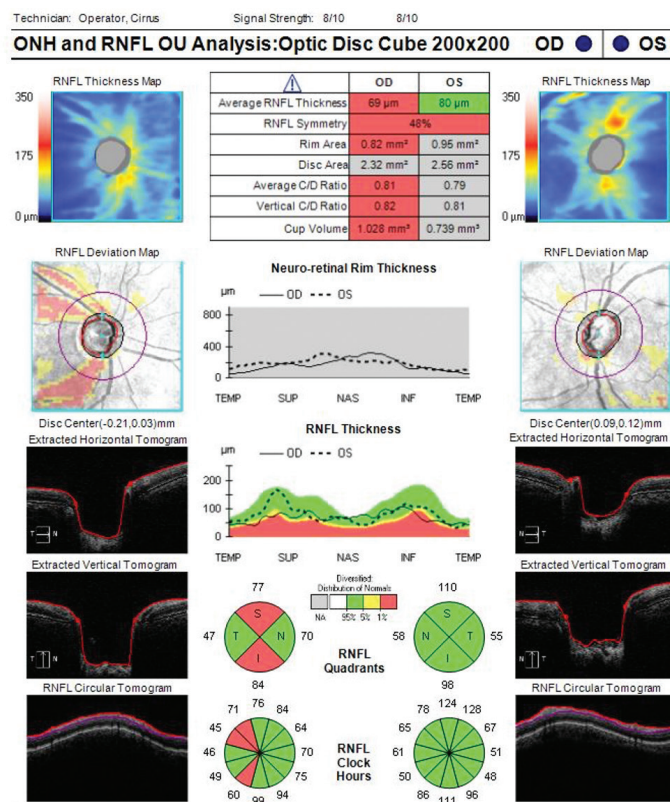
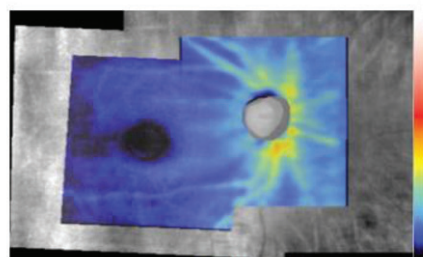
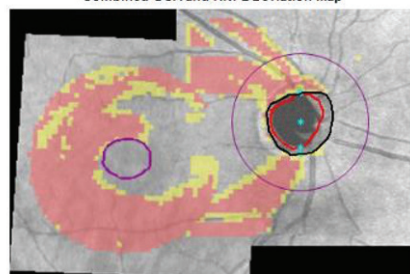


Figure 5. The patient's ONH and RNFL analysis.

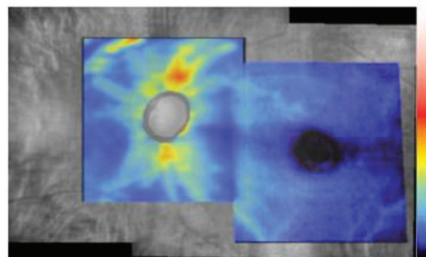
PanoMap Analysis: Right Eye



Combined GCA and RNFL Deviation Map



PanoMap Analysis: Left Eye



Combined GCA and RNFL Deviation Map

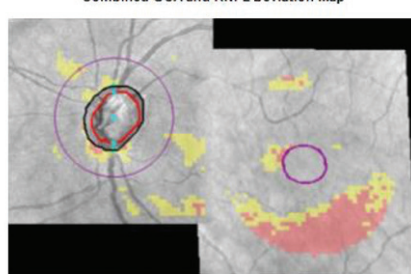


Figure 6. The patient's PanoMap analysis.

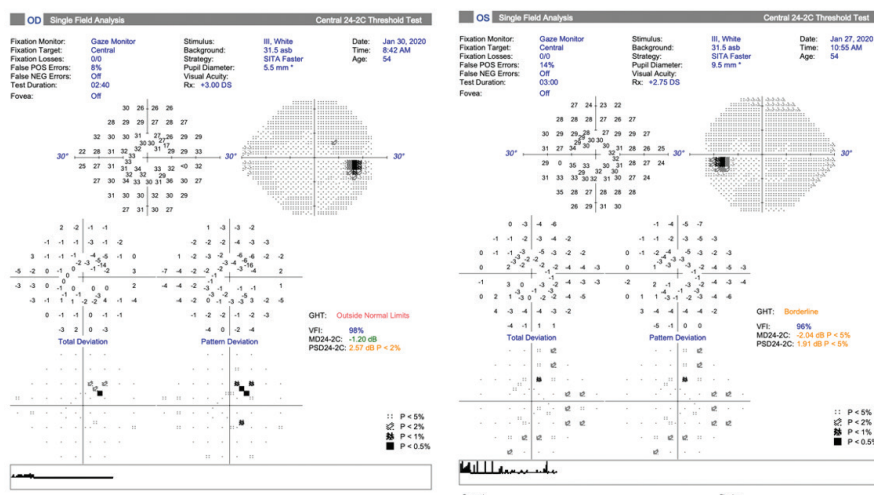


Figure 7. The patient's visual field analysis.

may even be the beginning of field loss in both hemifields, which would be even more bothersome. This patient needs significant IOP reduction. I offered him SLT, but he wanted to try medical management first. We started him on latanoprost, but we quickly escalated to adding netarsudil. We were able to bring down the pressures in both eyes to the low teens.

Dr. Radcliffe: One thing that jumps out to me here is that I don't think SLT is a great option. All agents work better at higher pressures, but SLT has a bit of a floor. I find these two trabecular agents to be great at driving pressures into the low teens from the mid-teens. I think there you have two just very good options in a case like this.

Dr. Bacharach: Dr. Radcliffe, you bring up an interesting point. You mentioned that most classes of agents work better from a higher starting pressure. The one exception would be netarsudil. ROCK inhibitors seem to work regardless of the starting pressure, whereas most other classes of medicines work about a half millimeter less well for every millimeter of lower starting pressure. Netarsudil was the perfect drug to use in this patient because the pressures weren't that high to start. When you look at the data from the netarsudil/latanoprost fixed-combination study, researchers were able to triple the percentage of eyes reaching 14 mm Hg or below over the latanoprost arm.³⁹ If you use clinical trials as a guide to treatment and then individualize that treatment to the patient, netarsudil was the optimal choice.

Dr. Radcliffe: Excellent comments. I'd like to thank the faculty for their insights on personalizing glaucoma treatment in 2021. ■

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GLAUCOMA TREATMENTS IN 2021:

Personalizing Patient Needs

CME Release Date: November 2021
CME Expiration Date: December 2022

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License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession	Years in Practice	Patients Seen Per Week (with the disease targeted in this activity)	Region
___ MD/DO	___ >20	___ 0	___ Northeast
___ OD	___ 11-20	___ 1-15	___ Northwest
___ NP	___ 6-10	___ 16-30	___ Midwest
___ Nurse/APN	___ 1-5	___ 31-50	___ Southeast
___ PA	___ <1	___ >50	___ Southwest
___ Other			

LEARNING OBJECTIVES

Did the program meet the following educational objectives?

Agree

Neutral

Disagree

Describe the mechanisms of action of novel therapeutics and classes of drugs for ocular hypertension (OHT) and primary open-angle glaucoma (POAG)

Interpret the challenges and limitations associated with currently available pharmacologic treatment options for OHT and POAG

Evaluate monotherapy and combination regimens and **compare** which option is most likely to achieve each individual patient's goal IOP

Compare and assess the efficacy of novel therapeutics with traditional prostaglandins

PLEASE COMPLETE AT THE CONCLUSION OF THE PROGRAM.

1. Based on this activity, please rate your confidence in your ability to apply updates in personalizing glaucoma treatment in the clinic. (Based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident.)
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
2. Sustained-release glaucoma treatments are likely to help which group of patients the most?
 - a. Patients with ocular surface disease who are struggling with drop adherence
 - b. Patients on maximum medical therapy
 - c. Patients with advanced glaucoma who need significant IOP reduction
 - d. Patients with early stage glaucoma who need moderate IOP reduction
3. Which of the following nitric oxide-donating moieties improves trabecular outflow?
 - a. Netarsudil
 - b. Netarsudil and latanoprost
 - c. Latanoprostene bunod
 - d. Selective laser trabeculoplasty (SLT)
4. Which of the following is true about the relationship with corneal hysteresis and risk of glaucoma?
 - a. Lower corneal hysteresis is associated with an increased risk of glaucoma
 - b. Lower corneal hysteresis is associated with a decreased risk of glaucoma
 - c. Corneal hysteresis is not associated with glaucoma
 - d. Corneal hysteresis is the main predictor of propensity to glaucoma
5. A _____ reduction in IOP is necessary to reduce the risk of progression according to the Collaborative Normal Tension Glaucoma Study.
 - a. 5%
 - b. 20%
 - c. 25%
 - d. 30%
6. According to the real-world MOST study, what percentage of patients will experience hyperemia on ROCK inhibitors?
 - a. 5%
 - b. 20%
 - c. 30%
 - d. 40%
7. Which IOP-lowering therapy targets the uveoscleral outflow?
 - a. SLT
 - b. Minimally invasive glaucoma surgery (MIGS)
 - c. Prostaglandin analogs (PGAs)
 - d. ROCK inhibitors
 - e. None of the above
8. Which of the following statements about patient compliance and dosing is TRUE?
 - a. Compliance decreases with decreased dosage regimen and complexity
 - b. Compliance increases with decreased dosage regimen and complexity
 - c. Less frequent dosing results in worse compliance
 - d. There is more compliance with QID drop regimens than with QD drop regimens
9. When counseling patients on the potential side effects of ROCK inhibitors, which of the following talking points should be made?
 - a. Hyperemia is common, is not an allergy, and may improve with time
 - b. Any hyperemia is due to an allergy to the medication, and they will need to discontinue use
 - c. Systemic side effects are a concern, and you should not use it if you're pregnant or thinking of becoming pregnant
 - d. Verticillata is a potential concern and may impact their vision
10. You are seeing a 53-year-old woman who presents for routine exam. You note high IOP at 28 mm Hg in both eyes. She has an enlarged cup-to-disc ratio in both eyes as well as a family history of glaucoma. She desires therapy with a drop, and she wants to minimize her dosing schedule. Which of the following is a first-line agent for this patient?
 - a. Carbonic anhydrase inhibitor
 - b. PGAs
 - c. Latanoprostene bunod
 - d. Alpha-adrenergic agonists
11. All of the following are mechanism of actions of netarsudil EXCEPT:
 - a. Increased aqueous humor production
 - b. Increased trabecular outflow
 - c. Decreased episcleral venous pressure
 - d. Decreased trabecular outflow
12. Sonia, a 50-year-old newscaster, presents for a routine exam, complaining of blurry vision. Her IOP is 26 mm Hg in her right eye and 24 mm Hg in her left. She has no family history of glaucoma and normal central corneal thickness. Her OCT is unremarkable, but her visual field reveals an inferior defect on the macular cube on her right eye. She's diagnosed with glaucoma, with a target pressure in the low teens. Her job is unpredictable, causing her to work odd hours, and she is frequently on camera. What first-line treatment might be most appropriate for Sonia?
 - a. Latanoprostene bunod
 - b. Latanoprost
 - c. OMNI
 - d. SLT
13. Dan is a 65-year-old man with diabetes, hypertension, and moderate glaucoma. He is on combination netarsudil and latanoprost for IOP control with mixed success. He is not always adherent to therapy, causing his pressures to range from 8 mm Hg to 17 mm Hg. He presents complaining of reduced visual acuity, which is due to a visually significant cataract. His current pressures are 19 mm Hg in both eyes. What is the next treatment step for this patient?
 - a. Cataract extraction, IOL implantation, and MIGS
 - b. SLT
 - c. Sustained-release bimatoprost
 - d. Trabeculectomy

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CE/CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom ____ Yes ____ No

Probability of changing practice behavior based on this activity: ____ Yes ____ No ____ No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (*check all that apply*)

- | | |
|--|---|
| <input type="checkbox"/> Change in pharmaceutical therapy | <input type="checkbox"/> Change in nonpharmaceutical therapy |
| <input type="checkbox"/> Change in diagnostic testing | <input type="checkbox"/> Choice of treatment/management approach |
| <input type="checkbox"/> Change in current practice for referral | <input type="checkbox"/> Change in differential diagnosis |
| <input type="checkbox"/> My practice has been reinforced | <input type="checkbox"/> I do not plan to implement any new changes in practice |

Please identify any barriers to change (*check all that apply*):

- | | | |
|---|--|--|
| <input type="checkbox"/> Cost | <input type="checkbox"/> Lack of experience | <input type="checkbox"/> Lack of resources (equipment) |
| <input type="checkbox"/> Lack of consensus or professional guidelines | <input type="checkbox"/> Lack of time to assess/counsel patients | <input type="checkbox"/> Patient compliance issues |
| <input type="checkbox"/> Lack of administrative support | <input type="checkbox"/> Lack of opportunity (patients) | <input type="checkbox"/> No barriers |
| | <input type="checkbox"/> Reimbursement/insurance issues | <input type="checkbox"/> Other. Please specify: _____ |

The design of the program was effective for the content conveyed.	____ Yes ____ No	The content was relative to your practice.	____ Yes ____ No
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The content supported the identified learning objectives.	____ Yes ____ No	The faculty was effective.	____ Yes ____ No
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The content was free of commercial bias.	____ Yes ____ No	You were satisfied overall with the activity.	____ Yes ____ No
		Would you recommend this program to your colleagues?	____ Yes ____ No

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

- | | |
|--|---|
| <input type="checkbox"/> Patient Care | <input type="checkbox"/> Medical Knowledge |
| <input type="checkbox"/> Practice-Based Learning and Improvement | <input type="checkbox"/> Interpersonal and Communication Skills |
| <input type="checkbox"/> Professionalism | <input type="checkbox"/> System-Based Practice |

Additional comments:

____ I certify that I have participated in this entire activity.

This information will help evaluate this activity; may we contact you by email in 3 months to ask if you have made changes to your practice based on this activity? If so, please provide your email address below.
