Supplement to Glaucoma TODAY AOC May/June 2015

CME ACTIVITY

Glaucoma Update: A Review of Current and Emerging Treatment Paradigms

Experts share insights and strategies for managing the growing number of patients with glaucoma.

Robert J. Noecker, MD, MBA
Nathan M. Radcliffe, MD
I. Paul Singh, MD
James C. Tsai, MD, MBA

DANNEMILLER Simply the Finest in Continuing Education™

A CME activity jointly provided by Dannemiller, *Advanced Ocular Care,* and *Glaucoma Today*.
Supported by Allergan.

Glaucoma TODAY AOC

Jointly provided by Dannemiller, *Advanced Ocular Care*, and *Glaucoma Today*.
Supported by Allergan.
Release Date: June 1, 2015.
Expiration Date: June 1, 2016.

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a live roundtable discussion held in February 2015 in San Diego, California.

INTENDED AUDIENCE

This certified CME activity is designed for glaucoma specialists, general ophthalmologists, and progressive optometrists involved in the management of glaucoma disease.

LEARNING OBJECTIVES

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

- Incorporate current glaucoma therapeutics into clinical practice
- Discuss the chemical structure and mechanism of action of topical glaucoma medications and evolving neuroprotective medications
- Effectively manage patients given issues of compliance with glaucoma medications
- Explain effective combined treatment therapies, including sustained-release formulations
- Understand the differences between bioequivalent drugs and name-brand drugs

STATEMENT OF NEED

Glaucoma is the leading cause of preventable blindness in the United States, and at least 3 million Americans have a form of the chronic disease.[1] Given the rapid increase in the aging American population, as well as increases in groups at high risk for glaucoma (most of which have an age component), the burden of disease related to this condition becomes more significant each year.[2,3] Additionally, there are several groups of people considered "high risk" for developing glaucoma:[1]

- Individuals with diabetes mellitus
- Individuals with a family history of glaucoma
- African Americans aged 50 years and older
- Hispanic Americans aged 65 years and older

Lowering intraocular pressure remains the stalwart of glaucoma therapy. Undiagnosed and suboptimally treated glaucoma results in irreversible vision loss. Patients may lose more than 40% of their optic nerve fibers before noticing a loss of peripheral vision.[4]

1. Centers for Medicare and Medicaid Services. January is National Glaucoma Awareness Month. Washington, DC, 2014.
2. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol.* 2004;122(4):532-538.
3. Fiscella RG, Lee J, Davis EJ, Walt J. Cost of illness of glaucoma: a critical and systematic review. *Pharmacoeconomics*. 2009;27(3):189-198.
4. National Eye Institute. Report of the Glaucoma Panel 2014. National Institutes of Health, 2014.

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 Dannemiller, *Advanced Ocular Care*, and *Glaucoma Today*. Dannemiller is accredited by the ACCME to provide continuing medical education for physicians.

Dannemiller designates this enduring material for a maximum of *1.5 AMA PRA Category 1 Credit(s).*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

METHOD OF PARTICIPATION

Participants should first read the objectives and other introductory CME/CE information and then proceed to the educational activity. To receive credit for this activity, please visit www.dannemiller.com/GlaucomaUpdate. Credit is provided through June 1, 2016. No credit will be given after this date. There is no fee to participate in this activity.

Should you have questions about this activity or are unable to retrieve the certificate, please e-mail cme@dannemiller.com, and a certificate will be e-mailed within 2 weeks.

FACULTY

Robert J. Noecker, MD, MBA
Ophthalmic Consultants of Connecticut
Assistant clinical professor of ophthalmology
Yale University
New Haven, CT

I. Paul Singh, MD
The Eye Centers of Racine & Kenosha
Racine, WI

Nathan M. Radcliffe, MD
Director of Glaucoma Service
New York University
New York, NY

James C. Tsai, MD, MBA
President, New York Eye and Ear Infirmary of Mount Sinai
Delafield-Rodgers Professor and System Chairman
Department of Ophthalmology
Icahn School of Medicine at Mount Sinai
Mount Sinai Health System
New York, NY

DISCLOSURES

In accordance with the Accreditation Council for Continuing Medical Education (ACCME), Dannemiller requires that any person who is in a position to control the content of a CME/CE activity must disclose all financial relationships they have with a commercial interest.

Robert J. Noecker, MD, MBA, has had a financial agreement or affiliation during the past year with Alcon, Allergan, Glaukos, Ocular Therapeutics, and SOLX.

Nathan M. Radcliffe, MD, has had a financial agreement or affiliation during the past year with Alcon, Alimera, Allergan, Iridex, and Glaukos.

I. Paul Singh, MD, has had a financial agreement or affiliation during the past year with Alcon, Allergan, and Bausch + Lomb.

James C. Tsai, MD, MBA, has had a financial agreement or affiliation during the past year with Aerie Pharmaceuticals.

Bernard Abrams, MD, content reviewer, and Jennifer Hodge, Dannemiller project manager, have no financial relationships with commercial interests. The *Advanced Ocular Care* and *Glaucoma Today* editors have no financial relationships with commercial interests.

To resolve identified/potential conflicts of interest, the educational content was fully reviewed by a member of the Dannemiller Clinical Content Review Committee who has nothing to disclose. The resulting certified activity was found to provide educational content that is current, evidence-based, and commercially balanced.

OFF-LABEL STATEMENT

Off-label statement provided: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, attendees/participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

DISCLAIMER

The content and views presented in this educational activity are those of the authors and do not necessarily reflect those of Dannemiller, *Advanced Ocular Care,* or *Glaucoma Today*. This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials on the subject.

To view the digital version of this print activity, scan the QR code or visit www.eyetube.net/cme-center and choose the appropriate title.

eyetube.net

Glaucoma Update: A Review of Current and Emerging Treatment Paradigms

Experts share insights and strategies for managing the growing number of patients with glaucoma.

Robert J. Noecker, MD, MBA: We begin our discussion with an overview of the state of glaucoma care. What are we seeing in our practices, and what have we seen in presentations and studies about the projected burden of disease in our population?

Nathan M. Radcliffe, MD: The US population is aging, and the strongest risk factor for glaucoma onset and progression is advancing age.[1,2] What is more, owing to advances in health care, people are living longer, many with chronic diseases. Those factors place three levels of burden on those of us caring for the aging population, particularly as insurers challenge us to work as efficiently as possible.

I. Paul Singh, MD: The baby boomers will cause a 50% increase in the number of people older than 65 years of age in the next decade, and we know the financial burden of glaucoma increases as disease severity increases.[1,2] Most likely, by 2020, more than 3 million people will have glaucoma, many of whom will be diagnosed with 20/50 visual acuity, which will worsen over time.[3] One study found a fourfold increase in direct ophthalmology-related costs as glaucoma severity increased.[4] We must identify at-risk patients earlier and diagnose and treat glaucoma earlier and more efficiently to decrease the potential cost in the aging population.

James C. Tsai, MD, MBA: Not only do we have an aging population with a higher risk for glaucoma, we also face the challenges of caring for patients—most of whom were diagnosed in their 50s and 60s—well into their 80s or 90s. The US Census Bureau estimates that more than 1 million Americans will be aged 100 years or older by 2050.[1]

Dr. Noecker: Our perspective has changed as life expectancy has increased. When I see a patient who is 55 years old with some visual field loss, I know I need to address that immediately with the patient.

Dr. Singh: Our standards for quality of life and patients' expectations are quite different now compared with when I came out of fellowship 10 years ago. Even patients aged 80 years or older want a good quality of life.

> "Numerous factors may influence how well a patient complies with therapy."
> — *Nathan M. Radcliffe, MD*

Dr. Tsai: Vision is still critical for older patients, even if they are homebound. Much of our training on how to manage elderly patients and what to provide for them in terms of services has totally changed. Expectations are different.

Dr. Radcliffe: An interesting question to ask patients is, "How long do you plan on living?" Their answers will frame their treatment expectations. Someone who has lived 10 years longer than either parent will feel differently about the future than someone whose parents lived well into their 90s. I think that helps you formulate a treatment plan with the patient.

Dr. Noecker: That is a good point. The aging of the baby boomers used to be a theoretical problem, but it is now a reality. There is no shortage of glaucoma patients. It is a bit overwhelming, particularly when we consider we may need to absorb 10% more patients next year. It is a huge demographic shift. How do you manage the volume of patients you need to see?

Dr. Radcliffe: I increase the follow-up interval for people who are at low risk for progression, so that I can use my time and resources taking care of those who are at high risk.

Dr. Singh: That approach underscores the importance of staging the disease and determining how often to monitor someone. We must feel comfortable with that scenario.

COMPLIANCE CHALLENGES

Dr. Noecker: One of the most important topics in any discussion of glaucoma is how patients comply with their therapy and how that influences our treatments. Dr. Radcliffe, what are some of the barriers to compliance?

Figure 1. Even with prompts, such as cap color, patients may become confused about their medications.

Dr. Radcliffe: Numerous factors may influence how well a patient complies with therapy. Patients may fail to pick up their prescriptions, or they may encounter a problem with insurance coverage at the pharmacy. If that happens, they are immediately set off course. Often, they have difficulty getting any therapy after they have a problem at the pharmacy.

Even when patients obtain the prescribed medicine, there are challenges. We have ample data that tell us, in a given 2-week period, at least half of patients will have forgotten or missed at least one drop, if not more.[5,6] But it gets worse. Even if patients remember to use their drops, they miss their eye about half of the time, or when they do get the drop in, they deliver more than one drop. That mistake almost guarantees they will run out of their medicine before the end of the refill cycle.

Another issue is tolerability. Even if a patient has overcome all of the other hurdles, an adverse event, such as hyperemia or allergy, may mean he or she no longer can use that drug.

In my opinion, health literacy, particularly related to eye drops, is a salient issue. Even with prompts such as cap color, many patients do not know the name of the medication they are using, even when they have been using it for years. An incident that occurred in my practice underscores this issue. A patient placed the wrong cap (yellow, for timolol) on her prednisolone acetate (pink cap) bottle, causing confusion and an increase rather than a decrease in her intraocular pressure (Figure 1).

> "I agree that education is key to improving adherence and persistence."
> — *James C. Tsai, MD, MBA*

Dr. Singh: I agree that education is key to improving adherence and persistence. I would add that we may underestimate the impact of ocular comorbidities, such as ocular surface disease and dry eye, in our glaucoma patients. We tend to attribute dry eye symptoms to antiglaucoma drops, when, in fact, patients may already have underlying disease, contributing to their discomfort when using their drops.

Dr. Noecker: Dr. Singh, how do you detect noncompliance among your patients?

Dr. Singh: When I started practicing, I thought all of my patients were following my instructions 100% of the time. I now assume every patient is noncompliant. Instead of asking if they are still using their drops every night, I ask how often in an average week they miss a dose. I assume this happens, and I make it comfortable for patients to divulge that information. Since changing my approach, I have found more patients than I expected were missing doses. If a patient should be using a drop twice daily or three times daily and is consistently missing a dose a day, his or her pressures will be fluctuating significantly. Noncompliance is a huge burden on our practice. Education has helped minimize its impact.

Dr. Tsai: Patients are often afraid to admit they are not using their drops properly. In a study published more than a decade ago, my colleagues and I asked patients why they had difficulty complying with their prescribed treatment regimens.[7] They responded with 71 unique reasons, more than half of which were situational or environmental, such as forgetting to bring their three-times-daily drops to work or forgetting to bring their drops when traveling out of the country. These are real-world challenges.

Another challenge is when patients do not see the benefits of the drops, but they see the side effects. Studies show that some patients stop using their drops for a period, taking a "drug holiday," so to speak, without telling us because they do not want to disappoint us.[8] I like Dr. Singh's non-

confrontational approach, which helps patients feel okay about admitting they did not use their medications as prescribed. It is important to let patients know we care about them and want to work together to solve this problem.

Dr. Radcliffe: I am particularly concerned when patients take a drug holiday the 2 weeks before seeing me but use their drops the day before the appointment. They will have a favorable initial response to that therapy, and I will unwittingly congratulate them. If they do not understand how important consistency is, they may think this is an acceptable way to continue.

Dr. Singh: I am also concerned when patients run out of medications and do not tell us right away. In our practice, we found that some patients wait more than a week to call for a refill, pick up the drug from the pharmacy, and resume using it.

Dr. Noecker: I find that patients tend to be much more open with my staff than with me, so I have staff members ask them what time they last used their eye drops. If they cannot remember, I have to assume they did not use them that day. Then I can move on to devising a strategy to fix that situation.

We often compare antiglaucoma therapy to oral therapy for other chronic diseases states, such as hypertension and hypercholesterolemia. However, studies of eye drop instillation have shown it is difficult to use eye drops without overdosing.[9] In addition, according to some managed care studies of refill rates for antiglaucoma drops, it is not unusual for patients to refill their prescriptions only 7 months out of the year.[10] I have to conclude that many people are not receiving even the bare minimum of drug that they need. That can have a strong impact on their ocular health, and it may affect what I choose to prescribe.

Dr. Singh: Patients often do not understand the ramifications of fluctuating IOPs, either throughout the day or from day to day.

Dr. Noecker: Exactly. Over time, I have become less forgiving. The worst scenario is when a patient says, "I was doing great until last night when I ran out of my eye drops." In the old days, I might have said, "Well, try harder. and next time, I'm sure you will do better." These days, I have to consider what else I can do. In some ways, my practice is an intervention. When patients see that their doctor is concerned enough to add a medicine or perform a laser procedure, they also become concerned.

Dr. Radcliffe: I also was forgiving of those high numbers when a patient admitted to missing a dose; however, in a study looking at risk factors for visual field progression in treated glaucoma, researchers found peak IOP was the best predictor of progression.[11] In other words, that should not be a forgiven moment. We should take action and not the same action that led to that situation. For me, that indicates we need to change gears and talk about a more permanent intervention.

"Patients often do not understand the ramifications of fluctuating IOPs, either throughout the day or from day to day."
— I. Paul Singh, MD

STRATEGIES TO AID ADHERENCE

Dr. Noecker: Dr. Tsai, does the pharmacology of the eye drop or the dosing schedule make any difference in terms of what you prescribe?

Dr. Tsai: I prefer a morning or evening dosing schedule with a once-a-day drop. Even if a patient needs adjunctive therapy, I think using a drop at the beginning or end of the day is preferable. I ask patients to think about what will be easiest for them. If a loved one or caregiver is at home, I involve that person. If a patient is having difficulty instilling the drops because, for example, he or she has mild Parkinson's disease, I emphasize that this is not about independence. This is about making sure the drops are used properly, and asking for help is okay. The challenge is that many patients live alone, and no one is overseeing their medications.

Dr. Singh: Another source of confusion for some patients is when a pharmacist tells them to use the drop at bedtime, which many patients interpret as immediately before sleep. They become concerned if they fall asleep before instilling their drops. In some cases (third-shift workers, for example), the prescribed times may not match up with when they sleep. In these cases, I reassure patients that it is okay if they use their drops a couple of hours before or after the prescribed times, as long as they are instilled around the same time of day. With a prostaglandin analogue, I feel comfortable allowing that kind of flexibility, if necessary.

Dr. Noecker: I try to tie the dosing schedule to the patient's lifestyle. Most of our patients are taking antihypertensive medications, and almost all of those are dosed in the morning. That is a repeatable, easy schedule for patients to remember.

Dr. Singh: We performed a study in our practice (as yet, unpublished) in which we changed the dosing regimen. A subset of patients in the study had some periocular changes in pigmentation, some hyperemia, but not a true allergic

TABLE 1. BRAND-NAME VERSUS GENERIC: WHAT PATIENTS NEED TO KNOW

Brand Name	Generic
Only one company makes the product.	Multiple different companies can make the product. Each company may use different components in the solution.
The FDA requires multiple, large multicenter studies to prove safety and efficacy of the active and inactive medication.	The FDA only requires smaller studies to confirm at least 80% equivalence of the active molecule—no studies on the inactive ingredients.
The FDA has tight oversight over the inactive ingredients in the bottle – preservative, PH, buffering agent, solution and the bottle itself.	No FDA oversight on the inactive ingredients and bottle—they can affect the efficacy and tolerability of the drop. There is also variability in how the drops come out, depending on bottle construction.
With each refill, you will always get the same medication from the same manufacturer.	With every refill, you may get a different generic manufacturer who may use different components—efficacy and tolerability may change with a different company.

Courtesy of I. Paul Singh, MD

> "Studies show that keeping the drug on the eye longer is more effective at lowering IOP."
> — *Robert J. Noecker, MD, MBA*

reaction. We asked those patients to use their drops earlier in the day, at least an hour before bedtime, to use an artificial tear before sleep, and to wipe their eyelids. The patients who followed that regimen reported fewer side effects.

Dr. Tsai: I usually try to tie the dosing schedule with activities people tend to do regularly, such as brushing their teeth. That way, they are not instilling their drops as they are turning off the light to go to sleep.

Dr. Noecker: I generally start with a prostaglandin analogue, which has a favorable once-a-day dosing profile. Some patients need adjunctive therapy, however, and those agents typically have twice-a-day dosing profiles. I have found I must be quite specific with my instructions. To me, twice a day means 7:00 AM and 7:00 PM, but to someone else, it might mean 8:00 AM and 9:00 AM. We know what we think we are saying, but sometimes, the meaning is lost on the lay population, so I have become increasingly specific with my instructions, so we are all on the same page.

As for prescribing a drop at bedtime, we have to remember that some people go to bed at 6:00 PM, while others may go to bed at 3:00 AM.

Dr. Radcliffe, what do you tell patients about eye drop instillation?

Dr. Radcliffe: My technicians teach patients how to properly instill their drops. If I do not see a favorable response to the therapy, I ask the patient if the drop is stinging, and I look for eyelash growth. If the patient is using a drop that should sting or cause eyelash growth and that effect is not present or is unfamiliar to the patient, it could be because he or she is not using the drop.

Dr. Singh: If I am not confident that a patient will be able to instill a drop properly, I ask him or her to place a drop of an artificial tear in the eye while I watch. Patients who have a great deal of difficulty may not be the best candidates for topical antiglaucoma drops.

For other patients, I suggest instilling an artificial tear 5 or 10 minutes before using their antiglaucoma drops, just to practice. That step has helped some patients become comfortable with drop instillation. In addition, the artificial tear may help minimize some of the burning and stinging caused by the antiglaucoma drop.

Dr. Tsai: Patients often find it difficult to perform punctal occlusion correctly, so I tell them to close their eyes after instilling their drops. Stopping the blinking reflex for a couple of minutes minimizes the amount of drug that exits the nasolacrimal ducts.

Dr. Noecker: That also helps reduce systemic side effects. By employing these tactics, we do not necessarily have to eliminate a particular drug. In addition, studies show that keeping the drug on the eye longer is more effective at lowering IOP.[12]

Dr. Singh: Do you recommend a specific position?

Dr. Tsai: Ideally, patients should be reclining or lying on a bed, but if they are very busy, that may be difficult.

Dr. Radcliffe: My fail-safe technique is to have a patient lie on his or her back and put the drop on the closed eyelid on the side of the bridge of the nose and lie there for about 10 minutes. Gravity forces the drop into the eye.

COST VERSUS VALUE

Dr. Noecker: The 1,000-lb gorilla in glaucoma management is the issue of cost. How do you address this?

Dr. Singh: We place a value on anything we purchase in life. Whether it is a pair of shoes, a watch, a computer, or a car, we ask if the object is worth the price. When patients receive a prescription for a medication, they ask the same question: Is this worth the money? Again, education comes into play. We need to help patients understand the value of what they are getting.

Regarding generic versus brand-name drugs, we did an interesting study in my practice (as yet, unpublished). Twenty patients who were starting monotherapy for glaucoma received prescriptions for a brand-name medication. When they returned for their first follow-up visit, all of them were using the generic version of the prescribed drug, even though I had written "no substitutions allowed." When I asked them about this, they said the pharmacist told them the generic was exactly the same as the branded drug. Therefore, I wrote a one-page handout describing the objective differences between brand-name and generic drugs (Table 1). I gave each patient a copy of the handout along with a new prescription for the brand-name drug with "generic substitution permitted" written down. When they returned for their regular appointments, 13 of the 20 patients had decided to purchase the brand-name medication. For those 13 patients, the difference in cost between the brand-name drug and the generic was approximately $30. For the patients who stayed with the generic, the difference was about $65. When patients understand what they are getting, many will pay for the branded drug despite the higher cost.

Dr. Radcliffe: For some reason, we appreciate the value of brands such as Starbucks, but we tend to question the cost of a drug that should be even more important to us. This is a health literacy issue. We need to give patients some guidance early on and let them know that the drug we are prescribing is an intentional choice just for them.

In some cases, if I suspect a patient may have a problem getting the branded drug, I will write a paper prescription for the generic drug after e-Prescribing the preferred therapy. I do not want this to be a mindless decision. I want both of us to have thought about it and made an intentional decision. In my experience, with that approach, 75% or more of my patients are using the therapy that both of us want for them, and with a very small investment of time.

Dr. Tsai: My approach is to educate patients as much as possible. In some situations—patients who are sensitive to almost every medication, for example—I explain the differences between the branded drug and the generic. I mention that the pharmacy may contract with multiple manufacturers for the same drug, so consistency among the generic products may be suspect. Whereas with a branded product, we know who the manufacturer is and the exact composition of the drug. Armed with this information, patients can make an informed decision.

Dr. Noecker: Whether I prescribe a branded or a generic drug, I emphasize to patients that I take glaucoma very seriously. Patients come to us as quality providers, to get our opinions. They can read about drugs on the Internet, they can talk to their friends, but at the end of the day, they still want to hear what our opinion is. That is our value.

I usually like to tell my patients what our next step will be—an additional drug or laser treatment—if a therapy is not producing the expected results. I lay it all out to avoid surprises. I tend to prescribe the products with which I have the most experience. If we encounter a problem, we talk about it and decide on a compromise plan. I take a strong position, so patients know their treatment matters.

Dr. Singh: I think patients like to see that their doctors believe strongly in the products and technologies they recommend. Then, they are more likely to accept them.

SUSTAINED DRUG DELIVERY

Dr. Noecker: We have discussed the challenges of compliance with glaucoma therapies, which, for the most part, are topical eye drops. I would like to shift gears and discuss some interesting new treatments on the horizon and their potential to solve some of our problems with adherence and persistence. Dr. Radcliffe, will you kick off this discussion?

Dr. Radcliffe: Glaucoma is a chronic disease that would benefit from sustained therapy, yet we are using pulse therapy to treat it. Patients become confused with the regimen, have difficulty instilling the drops, encounter problems at the pharmacy, and sometimes develop side effects. Ideally, we would have drug delivery systems that can provide consistent dosing from day to day, week to week, and month to month. Once we can place a sustained dose of drug closer to the target and in a manner that interacts less with the rest of the body, that will be a tremendous leap forward in our battle against glaucoma.

Dr. Noecker: Dr. Singh, can you share an overview of the different strategies?

> "I think there are multiple parts of the eye where we will see medication being delivered to the target tissue with minimal side effects."
> *— I. Paul Singh, MD*

Dr. Singh: Several strategies are in development right now, some that have different vehicles that improve contact time on the ocular surface, which is somewhat impermeable to many medications.[13] I think we will start to see more drug delivery options along these lines. In fact, researchers are currently studying injectable sustained-release prostaglandin analogues, and bimatoprost (Lumigan, Allergan) is one of them.[14] The idea is to inject the drug-loaded device into the anterior chamber, where the medication is released slowly over 4 to 6 months. This delivery system eliminates concerns about compliance, and the side effect profile is minimal because most of the side effects from topical drops occur on the ocular surface and are caused by the vehicle.

In addition, studies of a punctal plug delivery system containing a formulation of latanoprost (MatiTherapeutics) are underway.[15] Unfortunately, punctal plugs present some challenges, such as moving in the eye, falling out, or causing irritation. The amount of drug delivered may also be variable.

Suprachoroidal drug delivery to the back of the eye is another avenue being explored,[16] as are injectable implants that can release drug over a year-plus time frame. So, I think there are multiple parts of the eye where we will see medication being delivered to the target tissue with minimal side effects. These delivery systems also take the variables out of patients' hands.

Dr. Tsai: Sustained-delivery mechanisms would guarantee a specific level of drug in the eye and, I am hoping, mitigate the side effects of the pulsed regimens. I am looking forward to approval of these devices so we can use them in clinical practice.

Dr. Noecker: Do you think these delivery systems will change the way you treat glaucoma?

Dr. Radcliffe: Very much so. I think we probably all have operated on some patients when it was unclear to us how much compliance was a factor in their set of problems. With the sustained release systems, we can take that off the table.

I also think a given IOP-lowering molecule can behave very differently when formulated or delivered differently. In other words, the molecule is always a function of its dosing schedule and its surface tolerability. Once we are putting the drug in the eye, dosing is not an issue. A 4-times-a-day agent becomes a once-every-4-months agent. We may find ourselves taking long-abandoned molecules, molecules that never could have worked well on the ocular surface, and finding new uses for them. This may be a tool that helps us narrow the gap between our safe topical therapies and invasive surgeries. I imagine they will become part of the therapeutic regimen for most of our patients.

Dr. Noecker: How will you decide when to switch a patient from topical drops to one of these sustained-release models?

Dr. Radcliffe: I think we will see an evolution as physicians and patients change the way they think about these therapies. I will probably start using sustained-release devices in obvious cases, as in patients with poor compliance or severe arthritis, but will quickly consider them a primary therapy, because this is the ideal way to treat glaucoma.

Dr. Singh: I agree that our treatment paradigm will likely shift as we see safety and efficacy data and become more comfortable with the implantation procedure.

Dr. Tsai: Even though I am looking forward to using these devices, my one concern is that patients will not return for their follow-up visits. Again, we will need to be vigilant with our patient education.

Dr. Singh: On the other side of the coin, in some ways, this therapy forces patients to come back, because, with education, they know they cannot just go to a pharmacy and pick up a refill. I think in that way, we have some control over that process.

Dr. Noecker: This discussion highlights one of the ways this therapy will change how we practice. Instead of wondering whether or not patients are using their drops, we will simply be asking if the drug has fully dissipated. We will need to find some new methods for determining this, because we will want to extend the treatment interval to tailor it to the patient's biology.

Dr. Singh: That is analogous to the treat-and-extend approach with intravitreal injections of anti-VEGF agents for age-related macular degeneration. I think the interval between treatments depends on the molecule and the site where these mechanisms are working.

Dr. Noecker: I am looking forward to having these sustained-drug delivery systems. That said, I think we are all experienced enough in treating glaucoma to know no magic bullet or panacea exists for all patients. Most people

need multiple therapies. If I can have a patient using one drop a day versus two or three by performing selective laser trabeculoplasty, I think that is time well spent. Our goal in glaucoma therapy has been to reduce IOP any way we can, even if a therapy causes some side effects. We have not been able to reduce the treatment burden with many of our therapies to help patients maintain their quality of life. I believe the sustained-release systems will not only lessen the treatment burden for patients but also deliver more efficacy than ever before. The technology is revolutionary, and I think it will change how we treat and monitor patients.

Dr. Singh: I will be curious to see how sustained-release devices will affect the cost of glaucoma therapy, not only the actual costs for the drugs but also the costs of missed medications. Will a therapy that does not rely on patients to administer drops in the eye provide better IOP control? And how will that affect the overall cost burden?

Dr. Radcliffe: I think we all agree there is nothing more costly than someone losing vision from glaucoma. Letting someone lose functional vision and fall out of the workplace takes the greatest toll on their quality of life as well as society. I remind myself that being aggressive is a cost-efficient way to treat glaucoma, because the alternative is more costly.

Dr. Noecker: I agree. Studies have shown the impact on quality of life and the cost to society from falls and car accidents involving the elderly with vision loss.[17] I have recognized this in my practice, as well. A patient may report falling down the cellar stairs, and far from being bad luck, the truth is the patient did not see the step. These types of accidents happen more in those with glaucoma, but patients do not always make the correlation with their poor vision. Those can be life-altering events that change how someone functions.

FIXED-COMBINATION DRUGS

Dr. Noecker: Dr. Singh, what is your position on fixed-combination drugs?

Dr. Singh: According to pharmacy data, out of all the classes of medications, combination medications have almost a 12% growth rate, year after year, more than prostaglandin analogues or individual agents.[18] I believe more doctors are using combination medications, because we have learned our target pressures need to be lower, and we have also learned the impact of multiple dosing regimens. We are trying to reduce the number of drops patients need and also minimize the potential for side effects. Personally, I am using them more.

Typically, I try the individual components first if I can, but if the glaucoma is more advanced, I may go right to a combination therapy. I believe combinations are useful to achieve target IOPs with the minimum number of drops.

Dr. Noecker: What is your opinion, Dr. Tsai, as a long-time combination expert?

Dr. Tsai: Making a therapy as easy possible for a patient to comply with is the key. As in other fields of medicine where combination agents are becoming popular, I use them to reduce the burden of using more drops. Often, I am just trying to get a patient to use one drop. If I have to tell the patient to wait 10 minutes and use a second drop, that will be even more challenging. Quite frankly, I think few of us have the luxury of bringing patients back to try one component and then the other, and then the combination. In our busy practices, combination agents allow us to very quickly reduce patients' pressures.

Dr. Radcliffe: I think we are moving more toward fixed combinations. According to the literature, a single agent added to a prostaglandin analogue produces a pressure reduction between 2 mm Hg and 4 mm Hg.[19] With the fixed combinations, the reduction is closer to 5 mm Hg or 6 mm Hg.[20] Before choosing a fixed combination for someone, I use risk stratification, considering how far from target the pressures are, how severe the disease is, and how much time I have to get pressures under control. If pressures are significantly out of control and the patient is likely a surgical candidate, a fixed combination will help me determine that more quickly. I am an advocate of fixed combinations. That is definitely where we are headed.

Dr. Noecker: Do you have any safety concerns with the fixed combinations?

Dr. Radcliffe: I do not. The safety profiles of the fixed combinations are predictable. If someone has an adverse event, I can usually determine which agent is causing it. In addition, there is rarely a doubling of side effects. Sometimes, there is some synergy, and the side effect profile is acceptable. I think the combinations help us get ahead of glaucoma.

Dr. Noecker: I have become increasingly comfortable with combination therapy. I typically use a combination agent after first trying a prostaglandin analogue. Certainly, if I know someone has an allergy to a component or a contraindication, then I use the single agents.

I am troubled by the push by some non-eyecare providers to use individual components instead of combination drugs. Even though it may seem the same as a combination, in the real world, that is not equivalent therapy, particularly when you consider the preservative load and the washout effect. I have found very few patients are successful using the individual components.

Dr. Singh: Even if the individual components are generic, they sometimes can be as expensive as a combination.

Dr. Noecker: Exactly. I think it produces diminishing returns, and, as a provider, I resist having that happen. Nothing is more frustrating than when I have someone in steady state on a combination, and then it is suggested I start breaking up the components. In glaucoma, we do not get re-dos.

Dr. Tsai: As I add more bottles, I am always concerned that will affect the refill rate on the previous drug. That is why I usually start with a prostaglandin and then quickly add a combination.

Dr. Radcliffe: The fixed combinations also have a role as replacement therapy for prostaglandin analogues, which is a change in our approach. I recall 15 years ago, if a patient could not tolerate a prostaglandin, the replacement was probably timolol, because of the once-daily dosing. If you look at the data, however, timolol does not have the same efficacy as the prostaglandins, while the fixed combinations typically do.[21] I risk-stratify when a patient cannot tolerate or is not suitable for a prostaglandin analogue. But in many cases, I use a fixed-combination drug as replacement therapy for prostaglandin-intolerant people.

Dr. Singh: I also prefer to use a fixed-combination drug for monocular treatments. Prostaglandin analogues tend to have side effects that are more noticeable in these patients, such as eyelash growth and pigmentation changes.

MEETING THE CHALLENGES

Dr. Tsai: We have heard how challenging the management of glaucoma is, particularly for patients to fully adhere to the therapy we prescribe to preserve their vision. I know it would be challenging for me, which is why I always try to envision how I would manage the type of regimen I am prescribing. Would I be able to adhere to it? We have discussed some of the strategies, such as fixed combinations, that help patients adhere to their regimen and some promising new types of therapies involving sustained-release drug delivery.

Dr. Singh: Glaucoma is a lifelong disease that is largely asymptomatic, and we appreciate the impact of visual field loss on a patient's quality of life and daily functioning. It is not only sufficient for us to realize that, but we need to educate our patients so they realize the impact of being noncompliant and not addressing their pressures adequately. Being able to educate patients to understand the ramifications of that loss is key, because as Dr. Noecker says, we do not have do-overs. Once you lose that nerve tissue, those ganglion cells, they are not coming back. Glaucoma is a multifactorial condition, so anything we can do to minimize the burden on patients, whether it is using monotherapy, combination medications, or a potentially different drug delivery system, will help them maintain control and vision in the long-term.

Dr. Radcliffe: Glaucoma is a tough disease that justifies an aggressive approach as we try to preserve our patients' quality of life. We should choose therapies that are aggressive but also support an enhancement or at least a sustaining of their quality of life. Minimizing therapies to help with compliance, choosing efficacious therapies that will help reduce the need for additional interventions, and then finally, treating glaucoma on its own terms with an agent that exists within the eye and on a consistent basis, will turn the tables on glaucoma and give our patients better quality of life.

Dr. Noecker: We have many options and opportunities to treat glaucoma, but we are still held back by some of the barriers we have been dealing with for decades. Hopefully, all of the advances in glaucoma therapy will not be nullified by outside forces that shift profits and costs to the patients in traditional glaucoma therapy. I think the future of glaucoma treatment is bright, and the way we treat glaucoma will be significantly different within the next few years. Thank you all once again for your great contributions. ■

1. Ortman JM, Velkoff VA, Hogan H. An Aging Nation: The Older Population in the United States. Current Population Reports. p25-1140. US Census Bureau Washington, DC. 2014.
2. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol.* 2008;53 (suppl 1):S3-S10.
3. The Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol.* 2004;122:532-538.
4. Lee PP, Walt JG, Doyle JJ, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol.* 2006;124:12-19.
5. Stewart WC, Konstas AG, Pfeiffer N. Patient and ophthalmologist attitudes concerning compliance and dosing in glaucoma treatment. *J Ocul Pharmacol Ther.* 2004;20:461-469.
6. Hennessy AL, Katz J, Covert D, et al. A video study of drop instillation in both glaucoma and retina patients with visual impairment. *Am J Ophthalmol.* 2011;152:982-988.
7. Tsai JC, McClure CA, Ramos SE, Schlundt DG, Pichert JW. Compliance barriers in glaucoma: a systematic classification. *J Glaucoma.* 2003;12:393-398.
8. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. *Ophthalmology.* 2009;116:S30-S36.
9. Kholdebarin R, Campbell RJ, Jin YP, Buys YM. Multicenter study of compliance and drop administration in glaucoma. *Can J Ophthalmol.* 2008;43:454-461.
10. Schwartz GF, Platt R, Reardon G, Mychaskiw MA. Accounting for restart rates in evaluating persistence with ocular hypotensives. *Ophthalmology.* 2007;114:648-652.
11. De Moraes CG, Juthani VJ, Liebmann JM, et al. Risk factors for visual field progression in treated glaucoma. *Arch Ophthalmol.* 2011;129:562-568.
12. Dubey A, Prabhu P. Formulation and evaluation of stimuli-sensitive hydrogels of timolol maleate and brimonidine tartrate for the treatment of glaucoma. *Int J Pharm Investig.* 2014;4:112-118.
13. Lavik E, Kuehn MH, Kwon YH. Novel drug delivery systems for glaucoma. *Eye* (Lond). 2011;25:578-586.
14. Franca JR, Foureaux G, Fuscaldi LL, et al. Bimatoprost-loaded ocular inserts as sustained release drug delivery systems for glaucoma treatment: in vitro and in vivo evaluation. *PloS One.* 2014;Apr 30;9(4):e95461.
15. Knight OJ, Lawrence SD. Sustained drug delivery in glaucoma. *Curr Opin Ophthalmol.* 2014;25:112-117.
16. Patel SR, Berezovsky DE, McCarey BE, et al. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. *Invest Ophthalmol Vis Sci.* 2012;53:4433-4441.
17. Bramley T, Peeples P, Walt JG, et al. Impact of vision loss on costs and outcomes in Medicare beneficiaries with glaucoma. *Arch Ophthalmol.* 2008;126:849-856.
18. Schmier JK, Hulme-Lowe CK, Covert DW. Adjunctive therapy patterns in glaucoma patients using prostaglandin analogs. *Clin Ophthalmol.* 2014;8:1097-1104.
19. O'Connor DJ, Martone JF, Mead A. Additive intraocular pressure lowering effect of various medications with latanoprost. *Am J Ophthalmol.* 2002;133:836-837.
20. Fechtner RD, Harasymowycz P, Nixon DR, et al. Twelve-week, randomized, multicenter study comparing a fixed combination of brimonidine-timolol with timolol as therapy adjunctive to latanoprost. *Clin Ophthalmol.* 2011;5:945-953.
21. Holló G, Thelen U, Teus MA, et al. Long-term outcomes of prostaglandin analog versus timolol maleate in ocular hypertensive or primary open-angle glaucoma patients in Europe. *J. Ocul Pharmacol Ther.* 2011;27:493-498.

INSTRUCTIONS FOR CME CREDIT

To receive *AMA PRA Category 1 Credit(s)™*, you must complete the Posttest and Activity Evaluation and mail or fax to Dannemiller Inc.; 5711 Northwest Parkway; San Antonio, TX 78249; fax: (210) 641-8329. To answer these questions online and receive real-time results, please visit www.dannemiller.com/GlaucomaUpdate. If you are experiencing problems with the online test, please e-mail us at cme@dannemiller.com. Certificates are issued electronically; please provide your e-mail address below.

Please type or print clearly, or we will be unable to issue your certificate.

Full Name (shown on your certificate) _____

E-mail (required) _____

Address _____

City _____ State_____ Postal/Zip_____

Phone (required) _____

Select your credential(s):

❑ MD

❑ DO

❑ Other: _____

❑ Specialty: _____

CME QUESTIONS

AMA PRA Category 1 Credit Expires May 2016

1. In the next decade, the number of people over the age of 65 will increase by what percentage, owing to the aging of the baby boomers?
a. 20%
b. 30%
c. 40%
d. 50%

2. According to Tsai and colleagues, which of the following categories encompassed more than half of the 71 unique reasons why patients had difficulty complying with their prescribed glaucoma regimens?
a. Situational/environmental factors
b. Medication regimen factors
c. Patient factors
d. Provider factors

3. In a study of risk factors for visual field progression in treated glaucoma, which of the following was the best predictor of progression?
a. Mean follow-up IOP
b. Peak IOP
c. IOP fluctuation
d. Standard deviation IOP

4. When prescribed a branded IOP lowering drug with generic substitution permitted, more than half of the patients in Dr. Singh's study chose the branded drug. What may have led to this outcome?
a. Branded and generic costs were the same.
b. A generic equivalent was unavailable.
c. The prescribing doctor educated patients about the differences.
d. The generic was not covered by insurance.

5. Among the sustained-release drug delivery systems currently in development for glaucoma, which of the following has the disadvantage of potentially moving in the eye or falling out?
a. Implants injected into the anterior chamber
b. Punctal plugs
c. Suprachoroidal implants
d. Long-lasting (1+ year) anterior chamber implants

6. What is the typical pressure reduction when a single agent is added to a prostaglandin analogue?
a. <1 mm Hg
b. 2 mm Hg to 4 mm Hg
c. >4 mm Hg
d. 5 mm Hg to 6 mm Hg

7. What is the typical pressure reduction with a fixed-combination antiglaucoma drug?
a. <1 mm Hg
b. 2 mm Hg to 4 mm Hg
c. >4 mm Hg
d. 5 mm Hg to 6 mm Hg

8. Which of the following is Dr. Radcliffe's preferred first alternative to a prostaglandin analogue in a patient who is intolerant of that drug class?
a. Beta-blocker
b. Carbonic anhydrase inhibitor
c. Fixed combination drug
d. Selective laser trabeculoplasty

ACTIVITY EVALUATION

The content was delivered effectively.
❒ Strongly Agree
❒ Agree
❒ Neutral
❒ Disagree
❒ Strongly Disagree

The activity was objective, balanced, and free of commercial bias.
❒ Strongly Agree
❒ Agree
❒ Neutral
❒ Disagree
❒ Strongly Disagree

The learning methods or assessments of this activity were effective and appropriate.
❒ Strongly Agree
❒ Agree
❒ Neutral
❒ Disagree
❒ Strongly Disagree

The content presented in this activity was useful to my practice.
❒ Strongly Agree
❒ Agree
❒ Neutral
❒ Disagree
❒ Strongly Disagree

This activity has provided me with the tools/knowledge I need to make changes to my practice.
❒ Strongly Agree
❒ Agree
❒ Neutral
❒ Disagree
❒ Strongly Disagree

Please indicate which of the following learning objectives have been met (Select all that apply)
"After completing this activity, I am better able to..." (select all that apply)
❒ Incorporate current glaucoma therapeutics into clinical practice
❒ Discuss the chemical structure and mechanism of action of topical glaucoma medications and evolving neuroprotective medications
❒ Effectively manage patients with issues of compliance with glaucoma medications
❒ Explain effective combined treatment therapies, including sustained release formulations
❒ Understand the differences between bioequivalent drugs and brand-name drugs

Please rate the following statements on the following scale: 1 negligible) to 5 (outstanding)
How would you rate your competence* on this subject prior to attending this activity?
❒ 1
❒ 2
❒ 3
❒ 4
❒ 5

How would you rate your competence* on this subject after completing this activity?
❒ 1
❒ 2
❒ 3
❒ 4
❒ 5
* "Competence" is defined as the ability to apply knowledge, skills, and judgement in practice (knowing how to do something)

Please identify how you will change your practice as a result of completing this activity: (select all that apply)
❒ I will improve my methods for determining diagnosis
❒ I will communicate more effectively with my patients
❒ I will implement/change office protocols/policies/procedures to better meet requirements
❒ I will integrate new pharmaceutical approaches into my patients' treatment
❒ I will integrate new nonpharmaceutical approaches into my patients' treatment
❒ I will reconsider treatment options I may have previously dismissed
❒ I will change the way in which I monitor my patients' response to treatment
❒ This activity validated my current practice; no changes will be made
❒ I disagree with the suggested changes; no changes will be made (please specify)
❒ Other (please specify)

Please indicate any barriers you anticipate in implementing these changes: (select all that apply)
❒ Cost
❒ Lack of opportunity (patients)
❒ Lack of time to assess/counsel patients
❒ Lack of consensus or professional guidelines
❒ Lack of experience
❒ Lack of resources
❒ Reimbursement/insurance issues
❒ Patient compliance issues
❒ I do not agree with suggested changes
❒ I do not anticipate any barriers to change
❒ Other (please specify)

How long have you been in practice?
❒ Less than 5 years
❒ 5-10 years
❒ 11-15 years
❒ 16-20 years
❒ More than 20 years

What is your current type of practice?
❒ Private
❒ Hospital
❒ Academic
❒ Other (please specify)

(Continued on next page)

ACTIVITY EVALUATION (CONTINUED)

How many patients do you typically see per week?
❒ I do not see patients
❒ 1-10
❒ 11-20
❒ 21-30
❒ 31-40
❒ 41-50
❒ More than 50

Of these patients, to what percentage does this activity apply?
❒ 0%
❒ 1%-20%
❒ 21%-40%
❒ 41%-60%
❒ 61%-80%
❒ 81%-100%

How did you hear about this activity? (Select all that apply)
❒ Publication Ad
❒ Email
❒ Word of mouth
❒ Social media
❒ Flyer
❒ Dannemiller website
❒ Other (please specify)

Do you have any topic suggestions that would help to address other educational needs you and/or your colleagues may have?

_____

_____

_____

Any other comments? Suggestions? Please let us know what you did or didn't like about this activity and how it can be improved!

_____

_____

_____

May we contact you to conduct a followup survey regarding this activity? The follow-up survey will take less than 5 minutes, and we will contact you via e-mail, unless otherwise indicated.
❒ Yes, please contact me
❒ No, thank you

Glaucoma TODAY
AOC