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June 2017

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ANNUAL GLAUCOMA ISSUE

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REVIEW NEWS
Volume XXIV • No. 6 • June 2017

Drugs from Dallas Compounder Linked to Vision Loss

Compounding pharmacies have stepped into the breach created by a lack of FDA-approved infection and inflammation prophylaxis for intraocular injection after cataract surgery. In the Dallas metropolitan area, however, one prominent practice is now trying to help a group of patients cope with the effects of what it says were injectable agents not prepared as represented.

Key-Whitman Eye Center, a practice with offices in Dallas and north Texas, has announced that some of its cataract-surgery patients who underwent routine procedures at the PRG Dallas Surgery Center between January 31 and February 21, 2017 developed vision problems after receiving intraoperative injections of a steroid/antibiotic compound.

According to Jeffrey Whitman, MD, president and chief surgeon of Key-Whitman Eye Center, his practice has identified 20 to 30 affected patients who had cataract procedures done at the physician-owned PRG Dallas Surgery Center, where Key-Whitman doctors, as well as surgeons from other practices, operate. "The way we were able to trace it back was that one doctor called in to advise that she had a couple of patients who were completely healed at three and four weeks, but they had developed decreased vision: These patients had noticed darkening in the center of their vision and no other symptoms. The doctor had them come in and get checked, and their corneas looked perfect. Their anterior chambers were clear. Their retinas looked good, so she sent them to a retina specialist to see if there was something we were missing," Dr. Whitman explains. More calls from patients noting the same visual symptoms followed—all of whom had gotten the antibiotic/steroid injection during the same three-week span.

"We only gave that compounded medication during that three-week period," says Dr. Whitman. "After that, we stopped using it and went back to our Imprimis product." The injectable medication the affected patients received has been traced to a single batch compounded at Guardian Pharmacy Services (a Dallas-based, FDA-inspected specialty pharmacy that has never been affiliated with a similarly-named national institutional and long-term care pharmacy service based in Atlanta, Guardian Pharmacy Services LLC, or its partner, Guardian Pharmacy of Dallas-Fort Worth).

The consulting retinal specialist noted a change to the ellipsoid layer in the eyes of affected patients that was only detectable via OCT. Dr. Whitman said the retinal doctors explained that they'd seen similar changes in about 1 percent of patients undergoing Jetrea injections for vitreomacular adhesion, but that these changes had developed within 24 to 28 hours of treatment—not three to four weeks.

"There's no example of this in the literature," observes Dr. Whitman. "There are some examples of the vehicle being toxic under certain circumstances, but there's no article or study. That's a hard thing to have to tell our patients."

Key-Whitman notified every patient who'd had the injection, once they had traced the source of the affected patients' visual symptoms. They examined them at no cost and then referred the patients with problems to retinal specialists for free evaluations. They alerted other practices using the PRG Dallas Surgery Center, notified Guardian Pharmacy Services and the FDA, and also established a telephone hotline for affected patients. The surgery center's legal counsel hired an independent pharmacist to study the compounded medicine at issue. "His thought was that the suspension was at a very high concentration, and he believed that may be what caused the retinal damage," Dr. Whitman reports.

Attempts to Reach Guardian Pharmacy Services were unsuccessful. "All they'll say is that they're studying it. I don't know what that means," says Dr. Whitman of the compounder, adding that Guardian Pharmacy Services is under a temporary restraining order from Dallas County Civil District Court that enjoins them from distributing or destroying any of the suspect medication and any related documentation. The FDA is also investigating, he says.

"We're hurt and angry at the pharmacy," says Dr. Whitman. "These are our patients. We don't do a lot of co-management, and so we'll see

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these patients forever." He adds that some of the patients have recovered to normal or near-normal visual acuity; some are improving; but others have not. "We are watching the OCT scans with particular interest. In the patients that get better, you can see a re-forming of the ellipsoid layer," he says.

To the best of Dr. Whitman's knowledge, no patients have filed suit at this time, and Guardian Pharmacy Services has retained legal representation. "We continue to communicate with our patients and let them know what the progress is. Our legal representative has met with plaintiffs' counsel because we want to work together," he says.

Georgia ODs to Administer Injections

In late March, the Georgia House of Representatives and Senate approved a bill (SB 153, formerly SB 221) that allows optometrists to administer certain injections. Following the approval of the state legislature, Georgia Governor Nathan Deal signed the bill into law on May 9.

The law states: "A doctor of optometry may administer pharmaceutical agents related to the diagnosis or treatment of diseases and conditions of the eye and adnexa oculi by injection, except for sub-Tenon's, retrobulbar, peribulbar, facial nerve block, subconjunctival anesthetic, dermal filler, intravenous injections, intramuscular injections, intraorbital nerve block, intraocular, or botulinum toxin injections."[1] In a statement from the Georgia Optometric Association, the GOA says the injections will likely be in the lid and/or to address warts and nodules.

Optometrists say they're in favor of the bill's passage because medications delivered via injection into the lid often have fewer side effects than oral medications. They add that the law will improve the medical treatment of diseases by giving patients easier access to care in areas not served by ophthalmologists.

"The bill allows optometrists to perform injections and other delicate procedures in and around a patient's eye or eyelid—procedures they simply aren't qualified to perform."
—Steven M. Walsh, MD

In order to administer these injections, optometrists must hold a current license and obtain a certificate showing that they've completed an injectables training program sponsored by an accredited school or college of optometry, consisting of a minimum of 30 hours.

However, there is certainly opposition to the new injection law. Steven M. Walsh, MD, president of the Medical Association of Georgia, recently voiced his concerns with the motion. "The bill allows optometrists to make injections and perform other delicate procedures in and around a patient's eye or eyelid—procedures they simply aren't qualified to perform," he says. "We should never cut corners when it comes to any aspect of our health care, but this is especially true when it comes to our eyes

and our vision."

He goes on to detail the potential dangers of these injections. "Any mistakes occurring during procedures that are conducted in or near the eye can have particularly dire consequences, including infections, blurred vision, hemorrhaging and loss of sight."

The GOA, led by President Ben Casella, MD, applauds the bill's approval. In an official statement, he states: "As the training for doctors of optometry continues to increase to keep up with advancing technology, it is essential for the state law to keep up as well. [This law] makes that possible.

"The process of treatment via injection has been taught, both didactically and clinically, in colleges of optometry for many years," Dr. Casella says in a separate statement. "Consumers in more than 15 states have access to doctors of optometry authorized to perform these procedures, for which the doctors have received intensive training."

In the latter GOA statement, Dr. Casella contends that the law will be a boon to the statein general. "Doctors of optometry graduating today may select where to practice based on their authorization to use the training they received during their extensive years of study," Dr. Casella says. "We want to ensure that Georgia remains pro-business and continues to attract the brightest and best in the profession of optometry." REVIEW

1. http://www.legis.ga.gov/Legislation/20172018/167640.pdf accessed 10 May 2017

Correction

In the May 2017 installment of Technology Update, the capsulotomy cutting time of the Zepto device is incorrectly stated as 3.69 seconds. The correct cutting time claimed by manufacturer Mynosys is 4 milliseconds.

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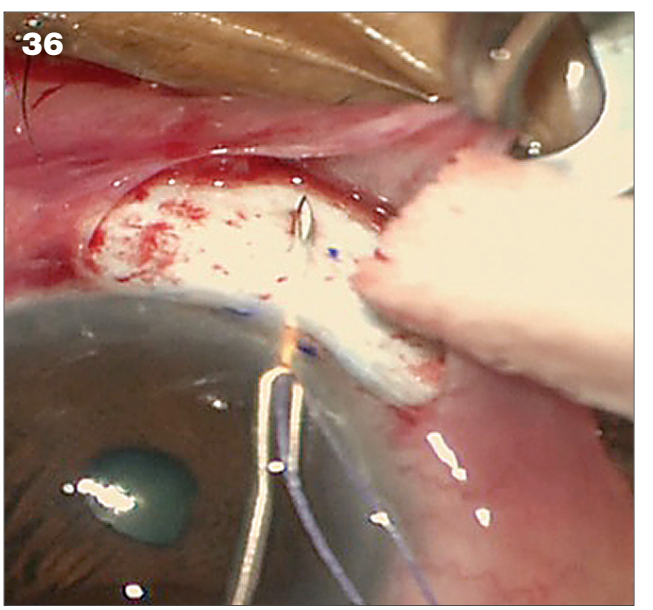

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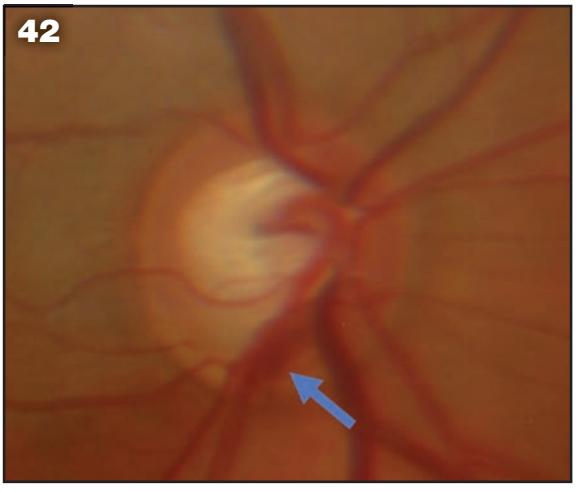

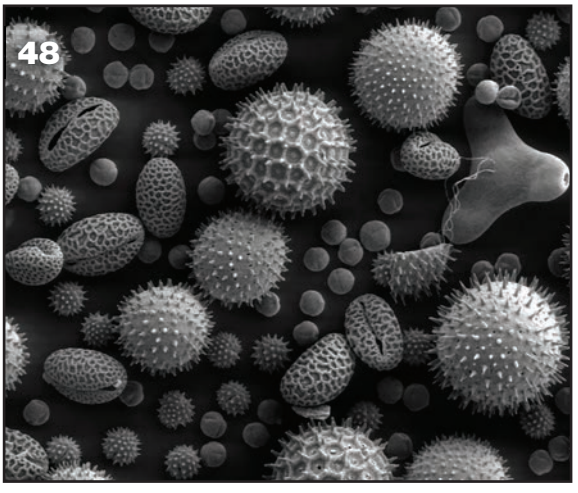

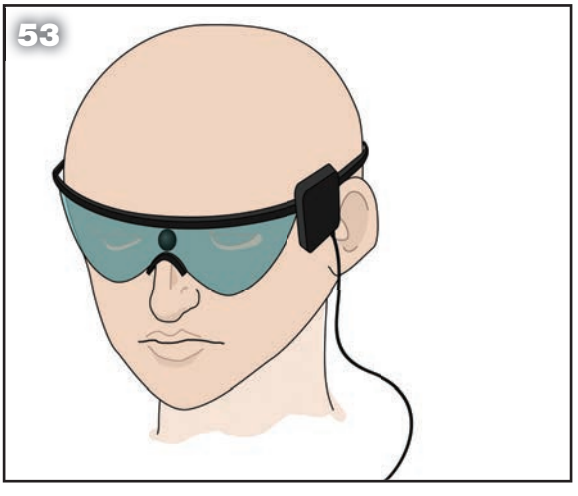

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Smartphone Apps: Aiding Compliance

A multitude of programs designed to help patients remember to take the right medication at the right time are now available.

Christopher Kent, Senior Editor

Patient compliance has always been problematic, especially when the patient has to manage multiple medications. Using technology to help ensure that patients use the right medication at the right time isn't a new idea, but with computerization and communication technology advancing rapidly, new ways to do so keep emerging. According to a recent article in *iMedicalApps*—an independent online medical publication for medical professionals, patients and analysts who are interested in mobile medical technology and health-care apps—a Google search for medication reminder apps turned up 272 options. The article noted that 109 of the apps were free. (However, only 33 of the 272 were available on both the Google Play and iTunes app stores.[1])

Here, we profile a number of these apps, and Rohit Krishna, MD, an associate professor of ophthalmology and director of glaucoma at the University of Missouri-Kansas City School of Medicine, who helped to create the popular app Eye Handbook (Cloud Nine Development, Overland Park, Kan.), shares some of his thoughts on this topic.

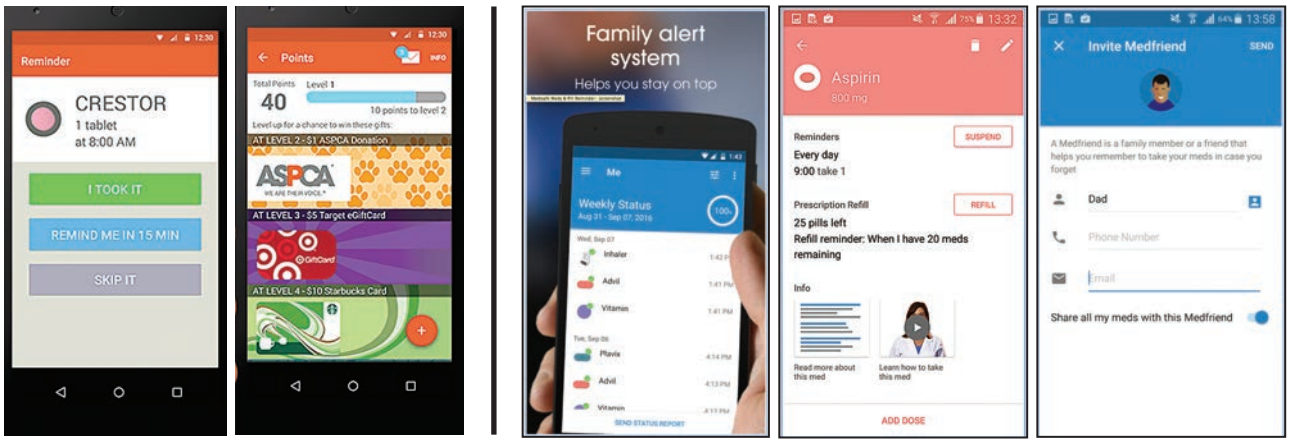
Putting Technology to Use

Dr. Krishna notes that many of the ideas for patient compliance aids come from other areas of medicine. "Ophthalmology is ahead of most specialties in terms of diagnostic tools, but when it comes to helping patients manage their medications, other specialties are ahead of us," he says. "Helping patients be compliant is an issue because 20 to 30 percent of prescriptions are never filled, and patients have plenty of trouble remembering to use drops—not to mention getting the right amount onto the eye when they do remember. I've seen estimates that poor adherence results in $290 billion a year in higher U.S. medical costs. On the other hand, some of these 'reminder' technologies have been shown to improve adherence by as much as 40 percent, which is a significant improvement.

"An important category of electronic patient management devices today is systems that use mobile phone technology," he continues. "That includes sending text message reminders, using smartphone apps and having interactive voice-response systems. Using mobile technology to help patients manage their health is referred to as 'mHealth.' It's becoming an increasingly popular way to help patients because smartphones have become ubiquitous, even in developing countries.

"In addition to providing reminders to take medications, a smartphone allows two-way communication with the patient, at the patient's convenience," he notes. "Smartphones are easy to use and have few limitations in terms of geography or time. Of course, contacting a patient by telephone is nothing new; doctors have been calling patients to make sure they're taking their medications or remind them of an upcoming appointment for years. But the computerized capabilities of smartphones allow them to help in ways that a noncomputerized phone can't. To that end, the Bill and Melinda Gates Foundation has given away a lot of grants to people to help them come up with clever ways to adapt mobile technology for health uses."

In addition to acting as a reminder, mobile devices can also use psychological principles to try to alter the patient's behavior in a positive direction.



Popular apps that can help patients remember to use medications include *MangoHealth* (sample screens, above, left) and *Medisafe Pill Reminder & Medication Tracker* (above right). More than 250 apps are available online, each with different advantages and limitations.

Dr. Krishna notes that one approach to modifying a patient's behavior is called *gamification*, which provides the patient with rewards for maintaining the desired behavior. "For example, the patient might receive virtual tokens that can be converted into actual prizes," he says. "One example of this is the HealthPrize system (HealthPrize Technologies; South Norwalk, Conn.) The patient can win tokens for everything from reporting each use of the medication to taking surveys and answering questionnaires. The app offers multiple types of incentives, including charity donations, gift cards, coupons for local discounts and health-related merchandise as rewards. The company says that its system has been shown to increase prescription refills by an average of 52 percent across all of the current platforms using the system. (You can find out more at Healthprize.com.) Measuring whether or not you're doing what you're supposed to do is a key part of this, and that will tie into some of the developments that still lie in the future, like a bottle with an electronic chip in it."

Although a few compliance apps use some variation on this idea, Dr. Krishna notes that he's not aware of any ophthalmologist who has tried using this system directly to influence patients—so far. "Right now ophthalmologists just reward you with good care," he says. "It's sad that you have to reward people to get them to do things they'll benefit from, but human beings do respond to being rewarded."

Some Popular Apps

Here are just a few of the apps available to your patients:

• ***MangoHealth & Pillboxie.*** These two apps are straightforward medication-reminder systems. Once you input the schedule the patient should follow, the phone provides a notification when it's time for an eye drop or pill and displays a picture of the medication that needs to be taken. (A picture can be very helpful if the patient is taking a lot of pills or using multiple drops.) MangoHealth, which uses the gamification principle to reward patients for following instructions, is free and can be downloaded from the Apple App Store or Google Play. (*See sample screens, above, left.*) Pillboxie is free for the iPhone at the Apple App Store. (For more information, you can visit mangohealth.com or pillboxie.com.)

• ***Memotext.*** Dr. Krishna says the Memotext system (Memotext; Bethesda, Md.) is a good example of a digital health application; it uses the patient's smartphone to send reminders and interact with the patient.

A 2014 study conducted at the Johns Hopkins University School of Medicine, Baltimore, tested Memotext's ability to alter behavior. After determining that 70 patients out of 491 were nonadherent to their once-a-day eye-drop medication regimen, 38 were randomized to use the Memotext system. They received daily messages, either text or voice, reminding them to take their medication. The control group received usual care. The median adherence rate in the 38 participants using the system increased from 53 percent to 64 percent ($p<0.05$). There was no change in the control group.

The study authors noted that one important aspect of this study was that this type of intervention is feasible in terms of the time and cost required from the ophthalmology practice. (The Memotext company estimated the cost to be approximately $20 per year per patient.) Also, the automated reminders were well received by the study participants.[2] (You can find out more at memotext.com.)

• ***Medisafe Pill Reminder & Medication Tracker.*** Created by Drugs.com, this app is free and available for both iOS and Android. According to *iMedicalApps*, it had the most functionality of the 272 apps they surveyed (14 different functions). For

example, Medisafe can bring family members into the process to remind the patient if a dose is missed. If the patient was due to take a drop at 7 o'clock but forgot, his phone would automatically turn on, and a relative would be alerted that he didn't take his pill. That relative could call the patient to remind him. Alternatively, the reminder could be automated using a text message or a personalized video of the relative reminding the patient to take the medication or eye drop.

The Wills Eye Glaucoma app includes educational videos, appointment reminders, data storage, a visual field tutorial and an IOP tracker.

• ***AlarMeds.*** This app is only available for Android. It allows customization of your dosing schedule, the medication image, the alarm and other features. According to *iMedicalApps*, AlarMeds' seven functions was the most of any app in the group of programs they surveyed that they considered basic rather than advanced. A simple version of the app usable with only one medication is free; a more advanced version is less than $2.

• ***Wills Eye Glaucoma App.*** Wills Eye Hospital in Philadelphia has created an app (free at the Apple App Store) designed to help glaucoma patients; it was developed by the Wills Eye Glaucoma Research Center in collaboration with Drexel University. It allows you to program your phone to beep when you're due for an eye drop, showing you a picture of the correct drop to take. It also provides educational videos, appointment reminders, medical and ocular data storage, a visual field tutorial and an IOP tracker.

A 2016 paper summarized a study evaluating the characteristics and attitudes of patients who were eligible to use the Wills Eye app.[3] Of the 50 subjects interviewed (mean age 59.5 ±17.3 years), 88.6 percent of them lived in a household with access to a smartphone or tablet, and 73 percent were receptive to using the automated reminder feature of the app. (Interestingly, however, many of those surveyed said they wouldn't use the app if they had to pay $3 for it.)

• ***MyEyeDrops.*** This option was created by the Singapore National Eye Centre and is available at the Apple App Store. Its reminder alarm shows the patient which drop to take and which eye to put it in, and allows multiple users and caregivers to be alerted of the reminders. It also provides a video showing the correct way to instill eye drops, and a diary to help dry-eye patients monitor the frequency and intensity of their symptoms.

What May Lie Ahead

Eventually, patient reminders may become unnecessary, thanks to two technologies already in the pipeline. The first is extended-release devices that will eliminate the need for drops. A number of different approaches are being tested, including injections of a depot into the subconjunctival space; putting a flexible ring that elutes medication onto the eye; contact lenses and punctal plugs that elute medications; and injecting something such as a nanoparticle or nanowafer inside the eye. Any of these, if effective, could eliminate the need for the patient to remember to take drops.

The other option is a feedback device that monitors factors such as intraocular pressure on an ongoing basis. This would allow treatment to be based on need. The patient might still need to use an eye drop, but use could be limited to times when a sign of trouble was detected. For example, researchers in Germany are developing an intraocular lens that incorporates an IOP sensor. Contact lenses with embedded IOP monitors are already available, although they're mostly being used for research so far.

To the extent that a drop reminder is still needed, the nature of reminder apps will probably change in the years ahead. For example, Apple is working on 'augmented reality' glasses that you might wear all day. It's not hard to imagine that when it's time to take your drops, the bottle will appear on the screen in your glasses, along with instructions explaining what to do.

"Today, we're in the midst of the digital revolution, with new technology appearing every year," notes Dr. Krishna. "Like other medical specialties, we can harness this technology to improve patient compliance. At the same time, it will improve our ability to monitor both the patient's compliance and soon, the status of factors such as IOP. All of this has the potential to have a great impact on patient care and produce significant cost savings for our health-care system." REVIEW

1. Study finds the best medication adherence medical apps. (no author listed) iMedicalApps.com, January 2017.
2. Boland MV, Chang DS, et al. Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: The automated dosing reminder study. JAMA Ophthalmol 2014;132:7:845-850.
3. Waisbourd M, Dhami H, Zhou C, et al . The Wills Eye Glaucoma App: Interest of patients and their caregivers in a smartphone-based and tablet-based glaucoma application. J Glaucoma 2016; 25:9:e787-91.

Classic beta blocker adjunctive therapy for the right patient at the right time[3]

The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

Indications and Usage

ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

For the patients who need incremental IOP reduction in a preservative free form[6]

Preservative-Free

TIMOPTIC® in OCUDOSE®
(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION) (DISPENSER)

For the patients who need incremental IOP reduction in a once a day form[6]

Istalol®
(timolol maleate ophthalmic solution) 0.5%

References: 1. Alm A, Stjernschantz J. Effects on Intraocular Pressure and Side Effects of 0.005% Latanoprost Applied Once Daily, Evening or Morning. *Ophthalmology*. 1995;102:1743-1752. **2.** Brubaker R. Flow of Aqueous Humor in Humans. *IOVS*. 1991;32:(13)3145-3166. **3.** Obstbaum S, Cioffi GA, Krieglstein GK, et al. Gold Standard Medical Therapy for Glaucoma: Defining the Criteria Identifying Measures for an Evidence-Based Analysis. *Clin Ther.* 2004;26(12)2102-2119. **4.** Istalol [package insert]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2013. **5.** Timoptic in Ocudose [package insert]. Lawrenceville, NJ: Aton Pharma; 2009. **6.** Stewart W, Day DG, Sharpe ED. Efficacy and Safety of Timolol Solution Once Daily vs Timolol Gel Added to Latanoprost. *Am J Ophthalmol.* 1999;128(6)692-696.

US/TOP/14/0017(1)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock (see **WARNINGS AND PRECAUTIONS, 5.2**).

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated] should, in general, not receive beta-blocking agents, including Istalol.

5.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.5 Potentiation of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.7 Masking of Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.8 Contamination of Topical Ophthalmic Products After Use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION, 17**).

5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

ADVERSE REACTIONS

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (see **WARNINGS AND PRECAUTIONS 5.8**) Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

Rx Only

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Osaka, Japan 541-0046

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General*, *Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC: Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.

UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents*.)

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Donna McCune, CCS-P, COE, CPMA

Rules for External Ocular Photography

A look at the documentation and reimbursement of EOP.

Q What is external ocular photography?

A External ocular photography documents medical progress of the external eye, lids and ocular adnexa. Photographs record conditions and pathology of the adnexa, external eye and anterior segment more accurately than chart notes or drawings. They are used to track changes in patients' abnormal conditions over time.

Q Do third-party payers reimburse for this diagnostic test?

A Medically necessary photos may be covered. The key points that justify coverage include that the photos:

- provide additional information not obtained during the exam;
- aid in diagnosis and treatment of a disease or condition; and
- are taken to assist in assessing disease progression.

Photographs taken merely to document disease are typically treated as an incidental part of an exam and are not separately reimbursed.

Some Medicare contractors have published verbiage in local policies stating, "… this procedure should not be used to simply document the existence of a condition in order to enhance the medical record."

Q What CPT code is used to describe external ocular photography?

A CPT code 92285: External ocular photography with interpretation and report for documentation of medical progress, describes this service. For tear film imaging, CPT instructs providers to use 0330T.

Q What documentation is required in the medical record to support a claim for external ocular photos?

A In addition to the photos or proof that digital images exist, the chart should contain:

- an order for the test with medical rationale;
- the date of the test;
- the reliability of the test;
- the test findings (e.g., vascularization, opacity, defect, dellen, dendrites, neoplasm);
- comparison with prior tests;
- a diagnosis (if possible);
- the impact on treatment and prognosis;
- the signature of the physician.

Q What diagnoses support a claim for external ocular photography?

A Medicare local coverage determinations contain a variety of valid diagnoses for external ocular photos. The lists vary, but usually include diagnoses related to external and anterior segment diseases involving the lids, lacrimal system, cornea, conjunctiva, anterior chamber and iris.

Q Are there specific instructions regarding documentation with photos prior to eyelid surgery?

A Yes. Some Medicare contractors describe documentation expectations with photos prior to eyelid surgery. For example, a contractor's requirements might resemble the following:

"COLOR photographs are required to support upper eyelid surgery as medically necessary. The 'physical signs' documented must be clearly represented in photographs of the structures of interest, and the photographs must be of sufficient size and detail as to make those structures easily recognizable. The patient's head must be parallel to the camera and not tilted, so as not to distort the appearance of any relevant

finding (e.g., a downward head tilt might artificially reduce the apparent measurement of a MRD). Digital or film photographs are acceptable. Photographs must be identified with the beneficiary's name and the date."

Q What is the frequency of external ocular photography?

A Medicare utilization rates for claims paid in 2015 show that external ocular photography was associated with 1 percent of all office visits to ophthalmologists. That is, for every 100 exams performed on Medicare beneficiaries, Medicare paid for this service one time. The utilization rate for optometry is about the same. Data for commercial payers is not published.

Q How often may this test be repeated?

A There are no national limitations for repeated testing. In general, this and all diagnostic tests are reimbursed when medically indicated. Clear documentation of the reason for testing is always required. However, too-frequent testing can garner unwanted attention from Medicare and other third party payers.

Q Must the physician be present while this test is being performed?

A Under Medicare program standards, this test needs only general supervision. General supervision means the procedure is furnished under the physician's overall direction and control, but the physician's presence is not required during the performance of the procedure. Other payers generally agree.

Q What does Medicare allow for external ocular photography?

A CPT 92285 is defined as "bilateral" so reimbursement is for both eyes. The 2017 national Medicare Physician Fee Schedule allowable for 92285 is $21.17. Of this amount, $17.94 is assigned to the technical component, and $3.23 is the value of the professional component. Medicare allowable amounts are adjusted in each area by local wage indices. Other payers set their own rates, which may differ significantly from Medicare's published fee schedule.

External ocular photography is subject to Medicare's Multiple Procedure Payment Reduction. This reduces the

(Continued on page 69)

Treating with SLT First: The Pros and Cons

Christopher Kent, Senior Editor

Topical drops are still the favored primary glaucoma treatment, but there's plenty of reason to reconsider.

When treating glaucoma, most doctors have traditionally been taught to start with medications. If topical drops fail to achieve the desired reduction in intraocular pressure, then clinicians typically try laser trabeculoplasty, and finally—if necessary—resort to surgery. With the advent of selective laser trabeculoplasty several years ago, however, many surgeons realized that laser trabeculoplasty could be a legitimate first therapy. But while there's been a slow increase in the use of SLT as a first-line option, most new glaucoma patients still end up using topical eye drops first.

"That sequence is ingrained in many of our ophthalmology colleagues," says Hady Saheb, MD, MPH, an assistant professor of ophthalmology and director of resident research at McGill University in Montreal. "However, I think there's enough evidence supporting primary SLT that it's an option we can justifiably offer to our patients."[1,2]

Shan C. Lin, MD, professor of clinical ophthalmology and director of the Glaucoma Service at the University of California at San Francisco, notes that the main reason SLT is not utilized more often is that its efficacy is often mild. "It usually achieves about 20-percent IOP lowering, about the amount of one eye drop, and then its efficacy wanes over time," he says. "By one year, you have a number of failures; by two years 50 percent of patients or more have had their pressures go back up. By three or four years, almost everyone's pressures are back up. Of course, that limitation is counterbalanced by the fact that you can repeat the procedure."

How many doctors are offering first-line SLT to their glaucoma patients? "When I give talks on this to American audiences and ask for a show of hands, about 10 or 15 percent of ophthalmologists appear to be strong advocates of doing SLT first," says Dr. Lin. "I suspect the vast majority of us will mention it as an option, but not necessarily advocate it; we tend to use medications first. That's conservative and safe, and in my experience most patients prefer it, because when they hear about laser or surgery they're often a bit scared and concerned."

Dr. Lin notes, however, that there's a certain irony to ophthalmologists not recommending first-line SLT more often. "When I ask the same audience of doctors which they would prefer to start with if they themselves were diagnosed with glaucoma today, half of them usually raise their hands to indicate they'd choose SLT," he says. "I don't think it's that we're not advocating for our patients as we would for

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ourselves; I think it's simply easier to start with eye drops."

Why Try SLT First?

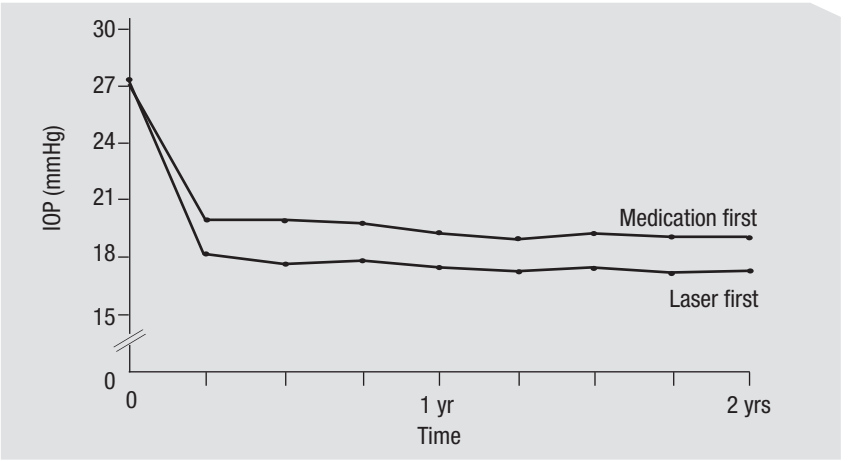
There's no question that not having to put in a drop every day—or at least having to put in fewer drops—would be seen as a benefit by nearly every patient successfully treated with SLT. But there are numerous other reasons to consider offering it to your patients as well. Those include:

• ***Studies support the use of laser before medications.*** Dr. Lin notes that an early study known as the Glaucoma Laser Trial comparing the use of argon laser trabeculoplasty to medications as a first-line treatment, sponsored by the National Institutes of Health, found that patients starting with ALT had better long-term outcomes than patients starting with medications.[3] "This study found that eyes that received ALT first had lower IOP at the long-term follow-up," he says. "They also had better cup-to-disc ratio scores and visual field scores, and their medication use was lower. Some of the ALT-treated eyes needed to go on medication after ALT, because the laser by itself couldn't lower the pressure enough in every patient; but at least those patients were using fewer medications at the end of follow-up.

"That study showed that even using the older argon laser, patients were better off doing the laser first," he says. "And today we can get the same effect using a better laser that's just as effective as the argon laser, one that doesn't cause the histological damage to the trabecular meshwork seen with the argon laser, and is repeatable."

• ***Doing SLT first may avoid the side effects of topical medications, including dry eye.*** "Doing SLT first avoids any issues with dry eye, which may be exacerbated by preservatives in the drops, especially in the age group we normally deal with," notes Sanjay Asrani, MD, professor of ophthalmology at Duke University School of Medicine, director of the Duke Eye Center of Cary and head of the Duke Glaucoma OCT Reading Center in Cary, N.C. "That's one of the issues that I have in the back of my mind when I suggest trying the laser first."

Glaucoma Laser Trial: Long-term IOP Control



The Glaucoma Laser Trial conducted in the 1980s and '90s compared primary argon laser trabeculoplasty to primary topical timolol. The laser showed better long-term IOP control.[3]

• ***Poor drop compliance puts the patient at risk.*** "Some studies have found that patients only use their drops about 50 percent as often as prescribed," notes Dr. Lin. "Other studies have found the number to be closer to 75 percent, but we want patients to use their drops 100 percent of the time. Furthermore, even when patients are trying to use the drops they often fail to get them into the eye, so the compliance studies could even be considered to be optimistic. At least when SLT is done the compliance is 100 percent."

Dr. Asrani says that if the patient is eligible for SLT or drops and asks for his opinion about which to start with, he tells them his preference would be to opt for the laser first. "Patients using drops occasionally go without the drops for a day or more," he says. "Whatever the reason, this can lead to a fluctuation of pressure that's not healthy. It can also stress patients out psychologically, feeling guilty or worrying about the consequences for their eyes. If they have the laser, this isn't an issue."

• ***SLT doesn't make the patient see himself as sick.*** "Using drops acts as a daily reminder for the patient that he or she has an eye disease," says Dr. Saheb. "I think being able to relieve patients of that burden does have some psychological benefit when you start by using SLT instead of drops."

At the same time, Dr. Saheb notes that this is a double-edged sword. "That also can have a downside," he notes. "The patient could end up believing that the laser cured his glaucoma—that he no longer needs to be followed."

• ***SLT is more effective when used first-line.*** Dr. Lin points out that—ironically—studies have found that the efficacy of SLT goes down as the number of medications the patient is already on increases. "SLT will be most effective in a virgin eye that has not received any medications yet," he says. "That's where you may see 25-percent IOP lowering, possibly more. If you're on maximal medications, which is the typical scenario in which many ophthalmologists consider performing SLT, it usually doesn't work well at all, or it has a minimal ef-

fect. You've already suppressed aqueous production and enhanced outflow so much through medications that the additive effect of SLT is reduced.

"If we follow the recommendation of the studies, including the big NIH study mentioned earlier, we should be offering it to our patients first-line—maybe even encouraging it, because it's so safe that you have practically nothing to lose," he says. "Furthermore, it seems to be more effective in the long run when used first-line, even if you have to add medications later on."

• ***SLT has a documented contralateral effect.***[4] "Almost every doctor who does this procedure will tell you that when the patient comes back, a large percentage of the time, the other eye's pressure is also lower," notes Dr. Lin. "We don't really know why, but that's not a bad thing."

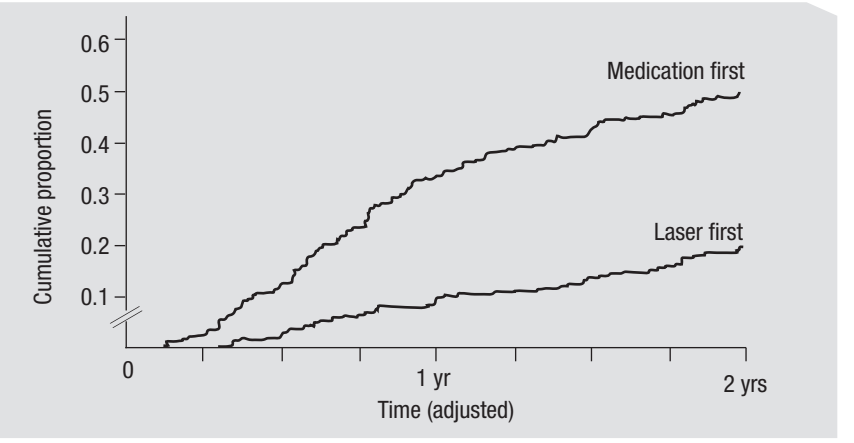
The Case for First-line Drops

On the other hand, there are a number of arguments for starting glaucoma treatment with topical drops:

• ***Efficacy***. Dr. Lin notes that some of the relative advantages of starting with medications have grown in recent years because of the more potent drugs now available. "Back when the Glaucoma Laser Trial was conducted, the options were not as effective at lowering IOP as today's prostaglandins, which on average will be more effective than SLT," he says. "Latanoprost usually lowers IOP about 30 percent. With laser trabeculoplasty, we're talking about more on the order of 20 to 25 percent IOP lowering, which is more typical for the second-line drugs like timolol, brimonidine and dorzolamide."

• ***No risk of a postoperative pressure spike.*** "Although SLT is very safe, there still is a risk of a pressure spike after the procedure," says Dr. Saheb. "Certain conditions are particularly at risk for this pressure spike—most importantly, pigment dispersion glaucoma. In those patients, SLT should be used with caution. In other types of glaucoma, a post-procedure pressure spike is a rare complication, but it's still one that patients and physicians need to be aware of. Reactivating uveitis is also a possibility if the patient has uveitic glaucoma."

Glaucoma Laser Trial: Use of Two or More Medications



The Glaucoma Laser Trial found that patients who were treated with primary ALT were using fewer medications long-term than those whose primary treatment was timolol.[3]

• ***Patient fears.*** Clearly, one reason surgeons often favor starting with drops is that many patients are put off by the idea of using a laser on their eyes. "In my experience, most patients will say that the laser sounds 'a little dangerous,' " says Dr. Lin. "That's ironic, because it's one of the safest things we can do."

• ***Patients are more motivated to return.*** "Some patients may disappear if they haven't been educated about their condition and their expected laser outcomes," notes Dr. Asrani. "If they don't seem to understand why they're getting the laser and the nature of the disease, I'd be quite hesitant to proceed with laser as the first-line treatment."

"If a patient truly has no preference and asks what I'd recommend, I'll say I have a slight preference for the topical medications," says Dr. Saheb. "I'm still a little concerned that the patient may be less motivated to return after successful primary SLT, even though I emphasize that glaucoma is never cured and follow-up is very important. If it works, it eliminates that daily reminder that the patient has an ongoing chronic condition and needs to return for follow-ups and diagnostic testing."

• ***SLT doesn't always work—and if it doesn't work, the patient may blame the doctor.*** "Even if the laser was done perfectly there will still be a 10 to 25 percent nonresponse rate," says Dr. Asrani. "The nonresponding patients may perceive this as surgeon incompetence. On the other hand, if patients don't respond to a drug, they usually don't think it has anything to do with the competence of the physician. This might influence some surgeons to just offer drops as primary treatment."

"In general, this is more likely to be an issue if you're seeing a patient for the first time," he adds. "If a patient has been with you for a while, not getting any effect is less likely to be seen as your fault."

Which Patients Choose SLT?

Although he's well aware of the advantages of using SLT as a first-line treatment, Dr. Lin says his patients only start with SLT about 10 percent of the time. "I usually do offer first-

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line SLT to my glaucoma patients," he says, "especially to younger ones who are busier and don't like the idea of using eye drops or anything artificial. They're working individuals who are more concerned about the advantages and disadvantages of the different treatment options. They go online and find that the drops may affect their heart or the color of their iris. They figure out that SLT is just about the safest thing we can do, so they're much more open to trying it.

"Older patients tend to be more conservative," he continues. "When you tell them they have to have a laser procedure or surgery—and they tend to equate the laser with surgery—they think of all the bad things that could happen. In contrast, younger people are more in tune with changing technology. Perhaps it's just because we're located in the San Francisco area, but our younger patients also seem to be more interested in being holistic. They try to avoid putting anything 'artificial' into their bodies, including medications. And of course, they like the convenience of not having to use eye drops."

Dr. Asrani says that in his experience, two types of patients are most likely to prefer SLT as a primary treatment option. "The first group is young patients who are not used to taking medications on a daily basis," he says. "They'd rather not take any if they can avoid them. The second group is the aged and infirm patients who are on so many medications they can barely keep up with them, and who may have a tough time getting drops into the eye."

Dr. Saheb says only a minority of his patients are fearful of the laser. "I make sure to call it a procedure, not a surgery," he says. "If a patient is still worried, I try to provide a little more information about the nature of SLT so the patient can make an informed decision. I point out that there are no blades or injections or needles, no sterile technique or operating room. However, there definitely is a subgroup of patients who are averse to any kind of procedure. I see no reason to try to persuade those patients, given that we have great medical options."

Educating the Patient Before Performing SLT

As with most procedures, making sure your patient has realistic expectations is crucial to a good outcome and a happy patient. These strategies can help:

• ***Present SLT as an opportunity to delay the need for medication, so the patient doesn't get the idea he's "cured."*** Hady Saheb, MD, an assistant professor of ophthalmology at McGill University in Montreal, says that presenting SLT this way helps ensure that the patient will return for follow-up visits. "I tell the patient that performing SLT helps delay the need to use medications," he says. "Saying that reminds them that this is a temporary effect, and there's a very high likelihood that they'll either need to repeat the laser a few years down the line or resort to using eye drops.

"To make sure the patient gets the message, I say this to the patient multiple times: when I'm offering the two options; on the day the patient receives the laser treatment; and again at the follow-up visit—especially if SLT worked well," he continues. "I say, 'You've had a good result. However, you need to remember that this is temporary. Your glaucoma is not cured; it's simply stabilized. We'll need to continue to follow you, and you'll likely need either a repeat of this laser or medications in the future."

• ***Make sure the patient understands what a realistic outcome may be.*** "Typically, the pressure lowering when the patient is treatment-naïve is 7 to 8 mmHg at the most," says Sanjay Asrani, MD, professor of ophthalmology at Duke University School of Medicine in Durham, N.C. "So if the patient's pressure is 40 mmHg and you need to get it to 18, make sure the patient understands that the laser alone will not be enough, and it won't eliminate the need for drops. Also, if you're using SLT as a second-line option, warn the patient that the pressure-lowering effect might be a bit less. And, make sure the patient understands that SLT does not always work; a small percentage of patients don't experience any pressure reduction and have to resort to using drops."

Dr. Saheb emphasizes the importance of not making SLT seem like a magic bullet. "Overselling SLT will only help convince the patient that he may be cured, putting follow-up visits at risk," says Dr. Saheb. "If you want to emphasize something, emphasize the need to return for follow-up visits."

• ***Warn the patient about the relatively mild post-laser symptoms.*** "The eye will probably be a little light-sensitive, a little sore, and might look a little pink for two to three days after the laser," Dr. Asrani points out. "Typically, I don't prescribe any post-laser eye drops such as steroids or NSAIDs. Instead, I recommend that the patient take frequent artificial tears to relieve any foreign body sensation that may occur."

—CK

Pearls for Patient Selection

One of the caveats for using SLT at any point in your protocol is that not every patient may be an ideal candidate. A few things to keep in mind:

• ***Be cautious about using SLT in pigmentary glaucoma.*** "Several studies have shown a paradoxical postoperative spike in IOP with these patients," says Dr. Lin.[6] "We're not sure why this happens. Maybe the greater pigment in the angle absorbs the laser energy more and causes actual scarring of the trabecular meshwork. Whatever the explanation, some of those patients end up needing surgery, so doctors should avoid using SLT in those patients."

However, Dr. Asrani believes that pigmentary glaucoma isn't necessarily a contraindication. "If you can titrate the power when treating pigmentary glaucoma you can avoid a pressure spike and get fairly good pressure lowering," he says. "In the past I was hesitant to do this, but no longer. Done at very low power, you'll avoid a post-laser spike and get an effective result."

• ***SLT is effective in pseudoexfoliation glaucoma, but watch out for the risk of an IOP spike.*** "SLT does work in these patients, but they may experience a postoperative pressure spike," says Dr. Lin.[7,8] "That may be related to the release of pigment, which also happens in pigmentary glaucoma."

• ***Avoid patients whose glaucoma is associated with inflammation.*** "This calls for caution on the part of the doctor, because sometimes a patient who has glaucoma that's associated with inflammation may present without any evidence of inflammation at the time of your evaluation," says Dr. Asrani. "For that reason, one has to be very careful when taking the history before performing SLT. Be sure to ask if the patient has ever had a red, painful, light-sensitive eye for days on end, is familiar with the words iritis or uveitis, or has taken steroids in the past for what may have been considered an infection by a doctor or by the patient. Also, look for telltale signs of inflammation when performing gonioscopy, such as any cell or flare in the anterior chamber.

"If the patient does have any underlying inflammation, SLT may stir it up," he continues. "In that situation the patient's eye pressure can become uncontrolled very quickly—in many cases enough that the patient will need incisional surgery right away. Therefore, it's vital to avoid treating patients who have inflammation as the cause of their glaucoma.

"If I'm not 110-percent sure that the patient is inflammation-free, I'll start the patient on a prostaglandin as kind of a litmus test," he says. "If the patient says the eye drop caused quite a bit of light sensitivity and severe redness and he just can't tolerate it, then I may be more concerned about the possibility of iritis. This trial is also useful as a way to determine whether the patient is able to manage a drop and remember to take it, and whether the drop has noticeable side effects. Finally, when the patient returns for the laser treatment, I ask if the patient is OK with taking the drop. Does she want to continue with the drop, or just do the laser and stop using the drop?"

• ***SLT can be useful in primary angle closure after a laser peripheral iridotomy.*** "Studies have shown that after you've opened a closed angle with a laser peripheral iridotomy, SLT will still cause a reduction in IOP," says Dr. Lin.[9] "Don't be afraid to consider using it in these patients."

• ***Don't underestimate the benefit of reducing IOP fluctuation.*** "Robert Weinreb's group, and others, have shown that diurnal fluctuation across 24 hours is dampened after SLT," notes Dr. Lin.[10] "Reducing 24-hour fluctuation in IOP has been associated with less glaucoma progression. So SLT may help the patient even if the pressure doesn't go down that much."

• ***SLT's pressure-lowering isn't as great in normal-tension glaucoma patients, but it may still make a difference.*** "Most doctors will tell you that SLT doesn't lower the pressure very much in normal-tension glaucoma patients," says Dr. Lin. "That's true; according to a number of studies, it lowers IOP 10 or 15 percent, compared to 20 to 25 percent with standard glaucoma.[11,12] However, it's still a statistically significant reduction. The doctor has to decide whether 10 or 15 percent is worthwhile for a given patient. Remember that the patient may also benefit from a reduction in the diurnal pressure curve."

• ***Don't worry about patients minding the need for repeat treatment.*** Dr. Asrani says in his experience, the laser typically works for at least two years. "For some patients, it lasts 18 months," he says. "For others, it's three to four years. In any case, I try to underpromise and overdeliver, so I tell my patients that we may have to repeat it in 18 to 24 months. Once patients have undergone the procedure,

they realize it's relatively simple; it's just a lens being held on the eye for a minute, without much discomfort, and there are no post-laser precautions or restrictions. So they don't hesitate if it needs to be repeated."

Pearls for Using SLT

When performing SLT, keep these strategies in mind:

• ***Treat 360 degrees, not 180 degrees.*** "Treating 360 degrees is more effective than partial treatment," notes Dr. Lin.[13] "Some doctors will only do half of the circle; they may come back later and do the other 180 degrees. Papers have shown that treating 360 degrees at one sitting is more effective than treating 180 degrees."

• ***Be certain you're lasering the correct target.*** Dr. Asrani notes that this is a common surgical error. "Intraoperatively, it's crucial to make sure you're lasering the trabecular meshwork, not Schwalbe's line, which sometimes is pigmented," he says. "You also must avoid lasering the ciliary body band, which sometimes can be mistaken for the trabecular meshwork. If the ciliary body band is lasered, the patient will get iritis and experience ciliary body spasm, with changes in refraction. The patient won't get any treatment benefit and will have quite a few side effects.

"This kind of surgeon error may be more common than we realize," he continues. "This happens mainly to patients who have a very lightly pigmented trabecular meshwork. So, when doing this laser procedure you want to have good gonioscopy skills and be very conversant with the landmarks. Always be sure you've identified the correct target before you start the laser.

"Thankfully," he adds, "if you laser Schwalbe's line, which is pigmented, you won't cause any side effects. But again, the treatment will be completely ineffective."

• ***Change the angle of the mirror when lasering the nasal and temporal quadrants.*** "When you're lasering the superior and inferior quadrants, the laser hits the trabecular meshwork end-on," Dr. Asrani points out. "However, when lasering the nasal and temporal quadrants, you have to angle the mirror so the beam of the laser hits the trabecular meshwork perpendicularly, not at an angle. If it hits at an angle, you're effectively only doing 180 degrees of SLT, not 360 degrees, because the lateral sides are barely skimmed with the laser. Moving the mirror and angling it is vitally important." Dr. Asrani adds that this is why surgeons should take a course or work with an experienced surgeon before attempting SLT.

• ***Be on the lookout for a postoperative pressure spike.*** Dr. Asrani explains that there are two different types of pressure spike that can sometimes happen after SLT. "The first kind of post-laser spike happens randomly to about 15 or 20 percent of SLT laser patients," he notes. "It's usually short-lived, and we have no way of predicting who's going to spike. For that reason we typically make every patient wait in the office after their SLT to confirm that there's no pressure spike. If there is, we bring the pressure back down before we let the patient go home.

"The other category of pressure spike is the kind in which the pressure goes very high within about a week," he adds. "Those patients—typically cases of uveitis-associated glaucoma that we missed—will have a bad headache and haloes around lights because the pressure has gone into the 50s and 60s. Those eyes will need incisional surgery. However, this is quite rare."

• ***Don't worry about diminished efficacy if you're adding SLT to a prostaglandin.*** "There's some concern about the efficacy of SLT when patients are already on prostaglandin monotherapy, because prostaglandins and SLT appear to work through a similar mechanism of action—increasing outflow—and perhaps through similar molecular mechanisms as well," says Dr. Lin. "However, at least one study found that SLT's efficacy is similar to initial therapy in this situation.[14] So having a prostaglandin on board—the most common first drop in the U.S.—does not appear to reduce the benefit of SLT."

• ***Be cautious about using steroid drops postoperatively.*** "In theory, steroid treatment after SLT may reduce its efficacy," says Dr. Lin. "I just use one steroid eye drop immediately after the procedure, as opposed to continuing it for several days. However, at least one study found that postoperative steroid drops didn't affect the efficacy of the procedure."[15]

• ***Consider offering SLT as a second option.*** "SLT acceptance among glaucoma patients is very high when it's offered in place of a second eye drop," notes Dr. Asrani. "Typically, the first-line drops are prostaglandins that are dosed once a day. A second eye drop will give you at least an additional 20-percent drop in pressure, but it's typically taken two to three times a day, which is not very practical for most people. So that's the point at which many patients are willing to try SLT, if they haven't already done it as the first-line treatment. I would definitely recommend trying it before advancing to a second eye drop."

Dr. Saheb agrees, noting that some patients may also be more receptive to the laser as a result of having taken a drop. "The first time you suggest treatment is always the biggest shock," he says. "I do find that some patients who start with medications and need further treatment are more open to laser treatment after a year or two of accepting their disease than they are upon initial diagnosis. Plus, they know how inconvenient drops can be. If the patient is having difficulty remembering to take a drop once a day, the idea

of taking one bottle once a day and a second bottle twice a day can be overwhelming. Furthermore, every time you add another drop, the likelihood of the patient remaining compliant and adherent goes down. And of course, SLT as a second treatment will avoid any side effects and preservatives that would be associated with additional medications."

Looking Ahead

Dr. Asrani notes that new SLT techniques are being developed that may make it easier to apply the treatment without gonioscopic skill and may cause even less post-treatment discomfort. "A recent paper from Michael Belkin, MD, in Israel, tested the efficacy of applying SLT externally to the sclera of the eye," he says.[16] "This approach was nearly as effective as the standard technique, and it might be more appealing to surgeons because it doesn't require gonioscopy skills. Of course, the popularity of SLT may also be affected by the advent of new, more effective drops, and new drug delivery techniques that might eliminate many of the downsides of using today's drops."

Dr. Lin adds that new drug options will also have an impact. "We're soon going to have options such as latanoprostene bunod, which is a modification of latanoprost, and rho kinase inhibitors like the one under FDA consideration from Aerie Pharmaceuticals," he says. "I think both of those will be approved this year, and they'll change the landscape. Studies show that latanoprostene bunod works even better than latanoprost.[17] Previously, if latanoprost didn't work, you might move on to SLT. Now you'll have another tool on the medication side that might lower pressure 33 to 35 percent. The patient doesn't do any more work if you switch drops; she's still using one drop a day, but she may get more efficacy from the same effort. So SLT's role may be modified as these new drugs become available." REVIEW

Dr. Saheb is a consultant for Alcon Novartis, Allergan, Bausch + Lomb, Johnson & Johnson Vision, Glaukos and Zeiss, and has research grants with Ivantis and Aerie Pharmaceuticals. Dr. Lin is a consultant for Allergan, Aerie, Eyenovia, AlEyeGN and Iridex. Dr. Asrani has no financial ties to any product discussed.

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Lowering IOP: Will First-Line Options Change?

By Kristine Brennan, Senior Associate Editor

Novel IOP-lowering drugs and delivery systems are coming. How will they fit into glaucoma treatment?

Since the approval of Xalatan (Pfizer) in 1996, the prostaglandin analogs have topped the list of IOP-lowering drugs for open-angle glaucoma and ocular hypertension. As novel medications and delivery systems await FDA approval, three ophthalmologists offer their insights into how these innovations might fit in with tried-and-true modalities.

First-line Standard: The PGAs

"Like most of my colleagues, I tend to use a prostaglandin as my first-line option," says Jason Bacharach, MD, medical director and founding partner of North Bay Eye Associates in Sonoma County, Calif. Tony Realini, MD, MPH, professor of ophthalmology and director of the glaucoma service, clinical research and the glaucoma fellowship at West Virginia University Eye Institute, says that for his newly diagnosed patients who don't elect primary SLT, generic latanoprost is his first choice. "The prostaglandin class of drugs provides the optimal efficacy, safety and convenience thanks to once-daily dosing—and lower cost with the generic formulation of latanoprost." Latanoprost also figures prominently in a recently released line of preservative-free compounded formulations called Simple Drops (Imprimis), ranging from the drug alone, to fixed-dose combinations of multiple drugs. The company says the combinations may increase patient compliance while reducing costs.

The prostaglandin analog class of drugs also includes bimatoprost (Lumigan; Allergan), travoprost (Travatan Z; Alcon), and tafluprost, which is available in a preservative-free formulation (Zioptan; Akorn Pharmaceuticals). As monotherapy, latanoprost,

Topical prostaglandin analog drops are widely accepted as first-line therapeutic agents for newly diagnosed glaucoma and ocular hypertension patients. New drugs and drug-delivery systems will soon vie for positions in the treatment paradigm, however.

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bimatoprost, and travoprost have all been shown to have comparable IOP-lowering efficacy.[1] The PGAs have virtually no systemic side effects, but possible ocular side effects include ocular/conjunctival hyperemia, eyelash growth, darkening of the iris, darkening of the periorbital skin and loss of periorbital fat.

For many patients, however, the advantages of the PGAs outweigh their disadvantages. They are generally the first-line therapy of choice before beta-blockers such as timolol; alpha-adrenergic agonists such as brimondine; carbonic anhydrase inhibitors such as dorzolomide; and the cholinergenic agonist pilocarpine.

Latanoprostene Bunod

"The reality is that only one drug so far has been better than latanoprost," says Dr. Realini. "That's latanoprostene bunod (LBN), and it's just a little bit better."

Latanoprostene bunod, a nitric oxide-donating prostaglandin F2 alpha analog, incorporates two mechanisms of action into one novel agent. Administered once daily, LBN is quickly metabolized into latanoprost acid and a nitric oxide-donating moiety called butanediol mononitrate. This new drug is thought to increase uveoscleral outflow via the latanoprost acid while also increasing the outflow of aqueous through the trabecular meshwork. "Greater IOP control with LBN is probably attributable to the nitric oxide moiety that's attached to the latanoprost," Dr. Realini explains. "When it's dosed, it breaks apart into standard latanoprost and nitric oxide. Latanoprost improves uveoscleral outflow, while nitric oxide works within the smooth muscle of the trabecular meshwork to increase trabecular outflow. These two complementary mechanisms provide an additive IOP reduction."

LBN 0.024% outperformed latanoprost 0.005% at lowering IOP in the Phase II Voyager study, which compared the safety and efficacy of LBN at various concentrations to latanoprost 0.005%. After 28 days, a 0.024% concentration of LBN reduced IOP by 9 mmHg in patients with a mean diurnal baseline IOP of 26.01 mmHg, representing 1.23 mmHg greater IOP reduction than in patients randomized to the latanoprost group.[2] A small number of study patients reported eye pain at the drop instillation site in both groups, with more LBN patients than latanoprost patients experiencing this. In Phase III studies, once-daily LBN demonstrated efficacy and safety, and was noninferior to[3] or better than[4] twice-daily timolol at lowering IOP in patients with open-angle glaucoma or ocular hypertension. Valeant, its subsidiary Bausch + Lomb and Nicox have announced a PDUFA date of August 24, 2017: The new drug's trade name is Vyzulta.

Despite LBN's superior IOP-lowering in comparison to

Table 1. Emerging Drugs

Agent	Main Mechanism of Action	Trial Results	FDA Approval Status
latanoprostene bunod 0.24% (Vyzulta)	Thought to increase uveoscleral and trabecular meshwork outflow.	Lowered mean IOP by 7.5-9.1 mmHg, outperforming timolol b.i.d.[3,4]	NDA to FDA
Netarsudil 0.02% (Rhopressa)	Thought to decrease episcleral venous pressure, increase trabecular meshwork outflow. May reduce AH production in eye.	Lowered IOP in eyes with mean baseline IOPs from 20.7-22.4 mmHg to 16.3-17.8 mmHg at three months (vs. 16.7-17.6 mmHg for timolol).[5]	NDA to FDA
Netarsudil 0.02%/latanoprost 0.005% (Roclatan)	Thought to be same as netarsudil alone, plus increase in uveoscleral outflow.	Lowered IOP by 1-3 mmHg more than either netarsudil or latanoprost monotherapy in eyes with maximum baseline IOPs from >20 to <36 mmHg.[7]	Phase III

A list of novel IOP-lowering drugs currently in the FDA pipeline. These agents all target more than one mechanism of action to lower intraocular pressure in patients with glaucoma or ocular hypertension.

latanoprost in trials, Dr. Realini says there's no sure way to predict the effect it will have on glaucoma practice patterns. "It's too early to tell how much of the market it will capture," he notes. "Based on what we know about these drugs so far, there may be an efficacy advantage to LBN over latanoprost, but I'm not sure whether that translates to being cost effective in the long run."

Three Mechanisms: Netarsudil

There are four ways that an IOP-lowering drug can do its job: increasing outflow through the trabecular meshwork; increasing uveoscleral outflow; decreasing episcleral venous pressure; and decreasing aqueous humor production. Netarsudil, a rho kinase (ROCK) and norepinephrine transporter (NET) inhibitor, is thought to target three of these. Dr. Bacharach, who has been an investigator for Rhopressa (Aerie Pharmaceuticals) says, "Besides increasing outflow from the trabecular meshwork, it appears from preclinical trials that it also lowers episcleral venous pressure. Interestingly, it also appears to reduce fluid production in the eye."

In the ROCKET 4 study of Rhopressa,[5] a trial required for the European regulatory approval process but not for the manufacturer's NDA to FDA, Rhopressa lowered IOP in eyes with a mean baseline IOP ranging from 20.7 to 22.4 mmHg to 16.3 to 17.8 mmHg at three months. Hyperemia occurred in 42.2 percent of study eyes, with most of it mild to moderate. Aerie has announced a PDUFA date of February 28, 2018.

Dr. Bacharach looks forward to integrating Rhopressa into his armamentarium primarily as a second-line therapy. "If you look at the Phase II study[6] [of which Dr. Bacharach is an author], you'll see that at lower starting pressures, i.e., below 24 mmHg, this drug worked equivalently and was non-inferior to latanoprost," he says. "It might be that in people who have low pressures there's an opportunity for this drug to be the first-line therapy because it's also dosed once daily. But in general, its most common position will likely be as a first-line adjunct to a prostaglandin.

"It's really complementary to the prostaglandins and appears to have an additive effect," he continues. "It's been demonstrated that patients who were on prior prostaglandin therapy, even with a washout, seem to get an additive effect when Rhopressa is added to the eye. The bottom line is that they're synergistic and they probably have complementary mechanisms. So theoretically, when you add Rhopressa to a PGA, you've affected every way there is to lower intraocular pressure. The uveoscleral outflow is addressed by the PGA: You've affected the other three mechanisms through netarsudil," he says.

A fixed-combination agent, Roclatan (Aerie) is behind Rhopressa in the FDA-approval process. Roclatan aims to target all four known mechanisms of IOP-lowering by harnessing the apparent additive effect of netarsudil and latanoprost. Roclatan has been demonstrated to have superior IOP-lowering abilities to either of its active components alone.[7] Dr. Bacharach believes that Roclatan has great potential as a first-line drug, based on its performance in trials.

Rhopressa represents a milestone in IOP-lowering therapeutics, according to Dr. Bacharach. "There hasn't been a new class of medicine in two decades," he says. "This class of medicines, and this drug in particular, is poised to be our first new option in a very long time. I use a variety of drugs as second-line options, and I think this drug will really launch to the top of my list for additive therapy."

All in the Delivery?

Even the safest and most effective IOP-lowering eye drop is devoid of therapeutic value if the script goes unfilled or the bottle sits in a medicine cabinet. Topical PGAs remain a therapeutic mainstay in the fight against elevated IOP, and many manufacturers

are developing novel delivery systems to overcome the biggest and best-known barrier to efficacy: poor compliance. "The prostaglandins are very effective and very safe, so it's going to be hard to beat them," says Dr. Realini. "One of the ways in which we might beat them is by finding a delivery system that allows us to reduce the dosing frequency and move the responsibility for dosing from the patient to the physician."

Ahmad A. Aref, MD, assistant professor and residency director at Illinois Eye and Ear Infirmary in Chicago, believes that the available and emerging IOP-lowering drugs leave little room for improvement: Instead, getting medicine to consistently reside in the eye is his current priority in glaucoma therapy. "I think that we've probably reached very close to our limit in terms of what we're going to be able to achieve with new medicated eye drops," he says. "I'm excited to hear about the new classes of medicines that are coming, but I would say that where things are really ripe for innovation is the question of how those drugs are going to be delivered," he says.

Dr. Aref notes that topical drops are too often an all-or-nothing proposition. "One thing that I've started to do in my office, if I'm questioning why someone's glaucoma doesn't seem to be under good control, is ask the patient to put an eye drop in at the office where I can watch them," he says. "Many patients are elderly and lack the physical ability to instill an eye drop in their eye; it can actually be a little scary to watch them attempting it in my office—not to mention multiple times per day at home without any assistance."

Dr. Aref, who recently reviewed emerging sustained-delivery systems for glaucoma drugs,[8] says that devices that don't penetrate the ocular surface may have an edge in terms of their safety profile. Devices in development include, but aren't limited to, a bimatoprost-eluting silicone-coated periocular ring (ForSight VISION5, Menlo Park, Calif./Allergan) made to sit between the upper and lower fornices of the eye; canalicular plugs that deliver travoprost (Ocular Therapeutix; Bedford, Mass.) and latanoprost-delivering punctal plugs (Mati Therapeutics; Austin, Texas). The above three technologies are currently in clinical trials.

"The bimatoprost ring and the punctal plug are both implanted on the outside of the eye and are very, very low risk since there's no incision; there's essentially no risk of infection on the inside of the eye. They're very safe," Dr. Aref says. The ring is available in an assortment of diameters and can deliver medication continuously for six months, although decreasing amounts of drug are released into the tear film over time. In Phase II testing, both the ring and topical timolol achieved IOP reduction of greater than 20 percent compared to baseline.[9] Although the ring didn't fully demonstrate noninferiority to timolol drops in that study,

Table 2. Emerging Drug-delivery Devices

Device	Description	IOP-Lowering	FDA Status
Bimatoprost sustained-release implant (Bimatoprost SR)	Intracamerally injected implant elutes bimatoprost. Biodegradable	Phase I/II range of dose strengths comparable to topical bimatoprost for 16 weeks.[10]	Phase III
Bimatoprost periocular ring (ForSight VISION5)	Flexible ring elutes bimatoprost.	Lowered baseline IOP by -3.2 to -6.4 mmHg over six months (vs. -4.2 to -6.4 mmHg for timolol drops).[9]	Phase II
Travoprost XR implant (ENV515)	Injected sterile nanoparticle implant with extended-release travoprost. Biodegradable.	Post-washout (prior PGA tx) eyes with 26.1 mmHG IOP at 8 a.m. had IOP drop to 19.5 mmHg at this time point for 11-month study.[11]	Phase II
Travoprost implant (iDose)	Titanium implant injected through clear corneal incision into AC. Removable.	Safety and efficacy trial assessing two different travoprost release rates.	Phase II
Latanoprost punctal plug (Latanoprost PPDS)	Silicone punctal plug that elutes latanoprost.	Trials for latanoprost plugs and for plugs eluting olopatadine for allergies underway.	Phase II
Travoprost punctum plugs (OTX-TP)	Activated by tear film, silicone hydrogel rods impregnated with drug swell to fit into upper/lower canaliculus. Fluorescein in plug aids visibility.	4.5 to 5.7 mmHg IOP reduction at 90 days (vs. 6.4 to 7.6 mmHg with placebo plugs and timolol drops).[12]	Phase II

A list of sustained-release drug-delivery devices in clinical trials. Though none of the emerging technologies listed here delivers new medications, they may prove innovative aids to compliance for those who cannot successfully follow a topical eye-drop regimen.

Dr. Aref points out that candidates for the ring would likely be patients who are unsuitable for drops due to poor adherence, making the rings a viable alternative. There were no unexpected adverse events, and subjects reported minor effects that commonly occur with bimatoprost use. The ring was retained in most study eyes for the six-month period and dislodgement was easily detected.

Also in the pipeline are sustained-release anterior chamber implants that deliver bimatoprost (Bimatoprost SR; Allergan) and travoprost (Travoprost XR; Envisia Therapeutics and iDose; Glaukos). The Bimatoprost SR, a biodegradable device currently in Phase III trials, demonstrated comparable IOP lowering in treated eyes at four different doses to fellow eyes treated with bimatoprost drops at 16 weeks and six months in data from a 24-month Phase I/II trial.[10] Transient adverse events occurred within two days of the injection in some implanted eyes, but no eyes needed the device explanted and there were no serious adverse events. Later-onset hyperemia was less common in implanted eyes than in the fellow eyes treated with bimatoprost drops.

Like the Bimatoprost SR, the Travoprost XR implant is biodegradable; the iDose is titanium and meant to be retrieved after it runs out of active travoprost.

"The injection-type therapy, i.e. the bimatoprost injection or the travoprost injection, seems to be more efficacious and last for a longer period of time," says Dr. Aref. "There's also no risk of dislodging it, compared to the ring or the punctal plug, which can be fairly easily dislodged. They don't seem to be as effective as medications given in an eye-drop form, though, so I think it's truly a judgment call in terms of risk versus benefit at this stage with the data that we have."

Dr. Aref notes that the injectable devices sidestep the issue of potential ocular surface damage from long-term glaucoma eye drop use. "We're now recognizing that very frequent exposure of the ocular surface to the preservatives in these eye drops can be very harmful over the long term, and may potentially even affect the outcome of glaucoma surgery, if a patient eventually needs it. Something like these injected implants would circumvent the potential exposure of the eye to preservatives, which can be very harmful," he says.

Dr. Aref also predicts that intracamerally injected IOP-lowering therapeutics will gain acceptance in light of the growth of injections to treat AMD. "I do think that patients with glaucoma are going to accept injection therapy for their disease because they likely have friends who get injections for macular degeneration, which have gotten a lot of publicity," he says,

Dr. Realini and Dr. Aref both wonder whether extended-release technologies will have an obvious target market, however. "In a patient who's well-controlled on a topical prostaglandin and who is not getting worse, is there any advantage to moving from a generic drop once a day to an expensive device?" wonders Dr. Realini. "What if they don't work quite as well as eye drops? Would the convenience factor be worth losing a point or two of IOP control? In some patients it might be. It's good to have options, but when we acquire them all at once, it's hard to know what to do with them," he observes.

Dr. Aref adds, "If somebody is fully adherent with their eye-drop regimen and not having any adverse effects, it's going to be very difficult to make a case for any of these devices." He does think that insurers might pay more up front to avoid the fiscal ramifications of uncontrolled glaucoma in patients who've clearly failed to benefit from IOP-lowering drops. "Sustained drug

delivery is worth considering for someone who acknowledges difficulty with adherence or has barriers to adherence, whether they are financial or physical limitations to being able to use eye drops. That could capture a significant percentage of patients," he says.

A Puzzle with Added Pieces

"The drugs that are in development and may be poised for approval in the coming months offer some advantages over our current first-line therapy of generic latanoprost," says Dr. Realini. "These are innovative products. They aren't yet another beta-blocker or PGA. But each of these drugs or drug-delivery systems also has limitations. It's not clear at this point that the balance of benefits and disadvantages will position any of these new products higher on the treatment spectrum than latanoprost."

Although it remains unclear where new drugs and devices will fit into the glaucoma treatment paradigm, Dr. Aref says that change is a given. "The way we traditionally think about treating glaucoma is all going to change," he states. "I think that physicians just need to be accepting of that, and be excited about it, because glaucoma is a field that really needs innovation. There's just so much more that our patients are going to need and expect over time." REVIEW

Dr. Bacharach is an investigator for Aerie Pharmaceuticals. Dr. Realini is a consultant for Alcon, Novartis, Inotek, New World Medical and Bausch + Lomb Dr. Aref has received a speaking honorarium from Novartis and is a consultant for New World Medical.

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An Update on MIGS Devices

Liam Jordan, Associate Editor

An in-depth look at the results and complications of the approved MIGS options.

With minimally invasive glaucoma surgery becoming increasingly popular, more and more devices are in the forefront of ophthalmologists' armamentarium. More options, however, means more decisions. In this article, we'll speak to users of several approved MIGS devices to help give you a sense of which device or procedure best fits your practice.

Glaukos iStent

The Glaukos iStent, like many MIGS devices, can be implanted during cataract surgery in the hopes of lowering intraocular pressure. Robert Noecker, MD, an ophthalmologist based in Fairfield, Conn., explains the optimal use of the iStent. "The best use is in allying it with the on-label indication, for mild to moderate glaucoma and those who need cataract surgery," he says. "In my experience, this is where it works well—for patients with relatively low pressures, or when we're being opportunistic for cataract surgery."

Dr. Noecker says that one advantage of the iStent is that surgeons are able to implant more than one device to further lower IOP. "It's a reasonable thing to do because there's a fair amount of data to suggest additive IOP lowering," he says. "If we can place these devices near collector channels, there's a higher chance we'll hit a great area to enhance." However, Dr. Noecker notes that reimbursement is still an issue when implanting more than one device. "The biggest barrier for this is reimbursement," he says. "I have done it separate from cataract surgery, and the patient has to pay for that portion because their insurance doesn't always cover it. So it depends on whether the patient wants to pay for another iStent."

In terms of implanting the device, Dr. Noecker provides some surgical pearls to maximize positive outcomes. "It's really all about the setup and patient selection," he says. "I also tend to use a fair amount of viscoelastic to keep the cornea clear and help make the trabecular meshwork angle more visible. The biggest error I see when teaching residents is that they tend to under-turn the head and microscope. You need a good point of attack so that the meshwork is almost vertical to make it a nice, easy, flat target. My motto is, in terms of visualization or tilting the head, it's hard to do it too much."

Once the device is implanted, Dr. Noecker offers some advice. "I always make sure I touch the mesh-

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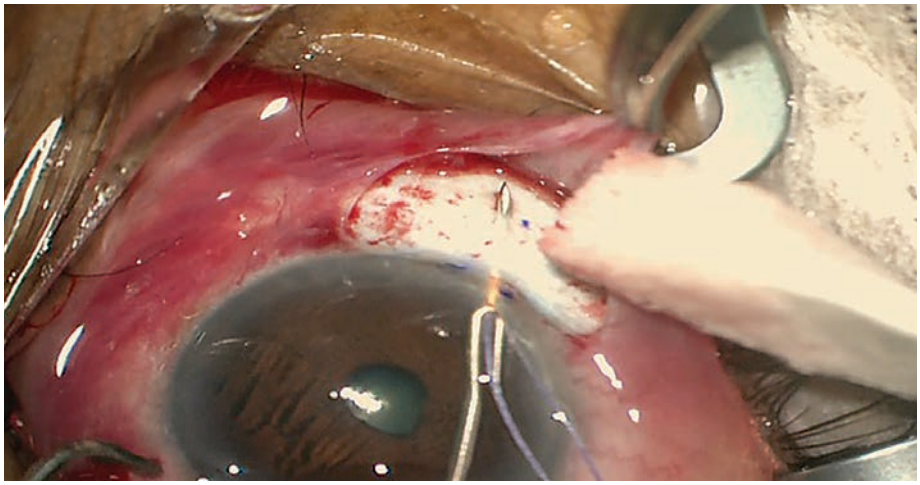
work with the blunt side of the stent. This helps you make sure you're deep enough, and it also indents the meshwork forward a bit," he says. "I think that makes it much easier to hit the target."



Implanting the Allergan XEN implant: "With this procedure, your first shot at delivering the device is your best one," says New York's Joseph Panarelli, MD.

When discussing postop complications, Dr. Noecker describes what to expect and how to react. "Honestly, complications are rare once you become familiar with the procedure. During the first three months of familiarizing yourself with the procedure, the complications usually come from surgeon error," he says. "The most common thing to worry about is, when you hit the canal, having your view obscured by blood. If a patient is on a blood thinner, this can be a bit of a problem. It's like striking oil—you feel good seeing it because it means you hit the target. It can get excessive, though.

"Obviously you can under-implant the stent," he continues. "When I'm teaching surgeons, I think that's an error. They're anxious to let go of the device before it's implanted. When you implant the iStent, there's a natural rotation of the eye that occurs, so you want to rotate the eye back to a natural position so there's no pressure on the injector. If there is pressure, the injector can flip the stent out of a good position."

Despite these concerns, Dr. Noecker is satisfied with the iStent. "In terms of few complications, I like the iStent," he says. "The chance of some really bad stuff happening is minimal. It's one of the lowest-risk glaucoma procedures that we do."

However, Dr. Noecker notes some reservations about the iStent, and what he would like to see change. "There's a real learning curve for implanting the device. Once you have it in a good position, you've nailed it, but achieving that can be difficult. The need to do intraoperative gonioscopy is limiting," he says. "Sometimes patients don't have a clear cornea to look through, and this can impair the viewing or placement of the device. So getting away from using intraoperative gonioscopy would be ideal."

Reimbursement is moderate, Dr. Noecker claims. "In other markets, I'm sure it's reimbursed well, but, for me, it's moderate," he says. "It doesn't pay as much as doing cataract surgery. The coverage has become very good in the past few years, and almost all payers recognize it and pay for it, but how much is variable depending on your market."

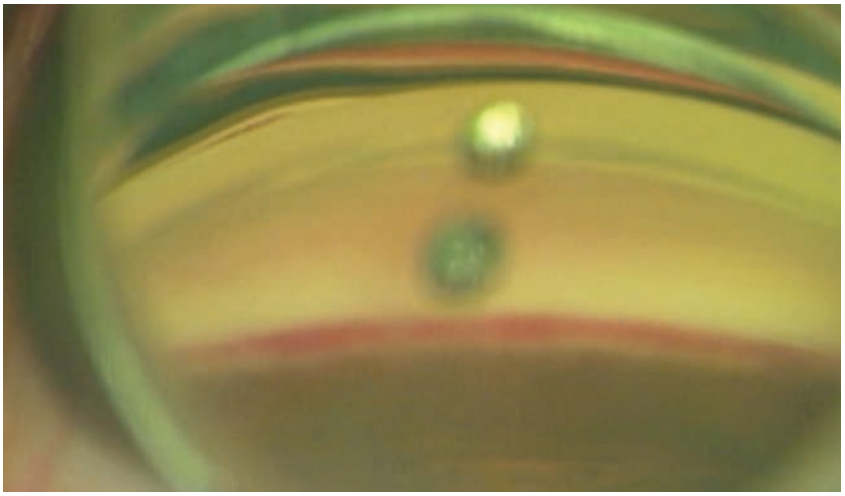
Alcon CyPass

Approved in late July 2016, Alcon's CyPass has proved to be another contender in the arena of MIGS devices. The device was approved in the United States based on results from the COMPASS clinical trial, and has been studied in clinical trials in Europe since 2009. Tsontcho Ianchulev, MD, MPH, of San Francisco, shares his experience using the CyPass.

In terms of patient selection, Dr. Ianchulev says that to ensure the best outcomes, it pays to follow the FDA guidance. "We try to treat those patients with mild to moderate glaucoma who are undergoing cataract surgery," he says. "Diligent patient selection is essential for the best outcomes. You don't want to go for end-stage or severe cases, which need more drastic IOP lowering. If you do it for patients with cataracts, you help those patients stay medication-free for two years and beyond." In the COMPASS clinical trial, 61.2 percent of 374 patients maintained mean IOPs between 6 mmHg and 18 mmHg at two years.[1]

Dr. Ianchulev also provides some advice for the procedure itself to maximize positive outcomes. "You'll definitely have a learning curve with this procedure," he avers. "It's probably five cases before you get the hang of it. It's a straightforward surgical procedure, but it's not trivial. As with other MIGS, you have to have some gonioscopy skill, be able to visualize the angle and implant the device correctly. Experience and practice make for the best outcomes."

Though the CyPass proved safe and effective in its clinical trial, you can still run into some problems. "The complications are generally mild, tolerable and, ideally, resolvable over time," Dr. Ianchulev says. "You have



Trabectome, after blood reflux. The procedure consists of the tip of the Trabectome unroofing the trabecular meshwork, increasing flow into the aqueous drainage system.

a little bit of inflammation, and in some cases you can have some reflux bleeding. None of it is all that consequential or interferes with the results we want."

In the COMPASS clinical trial, only 5.3 percent of the CyPass group (20 patients) underwent secondary ocular surgeries. Corneal edema associated with the surgical procedure resolved within the first postop month in 98 percent of CyPass group subjects. No cases of retinal detachment, pupillary block, endophthalmitis or hypopyon were reported during the study.[1]

Dr. Ianchulev also shares his thoughts on some ways to improve the procedure. "The device is not the easiest one to implant because visualizing the meshwork can be difficult, versus being able to implant it into the superciliary space," he says. "But I think it's pretty much where it ought to be compared to the other available devices. It's got a great learning curve surgically. On the other hand, we could improve the procedure by having it move towards treating the moderate-to-severe glaucoma population. Having a solution for trabeculectomy is where there is definitely room for development."

When discussing reimbursement for the CyPass, Dr. Ianchulev says, "It has its own CPT code, and Medicare will start paying for it if they haven't already. It's FDA-approved, so the code will be in the same ballpark as the other MIGS devices. It'll probably be reimbursed higher than cataract surgery. When it becomes fully reimbursable, it will definitely justify the clinical effort."

Allergan XEN Implant

Allergan's XEN Implant can be used either alone or in conjunction with cataract surgery to treat patients with mild to moderate glaucoma. Joseph Panarelli, MD, an ophthalmologist from New York, offers his experience using this implant. Dr. Panarelli describes his patient selection as an integral part of ensuring good outcomes. "The XEN implant can be used for a variety of patients as it tends to be a safe, rather straightforward procedure that produces a diffuse, more posteriorly directed bleb. I think we'll see that these blebs are at less risk for leaks, as well as infectious complications," he says. "I would consider using it in patients with mild to moderate glaucoma as either a standalone procedure or in combination with cataract surgery. I would even consider using it in ocular hypertension patients who are intolerant of medical therapy. But I hesitate to use this device in those with advanced disease, as it's difficult to achieve very low IOPs with it."

In describing the implantation procedure, Dr. Panarelli notes that he has yet to implant more than one device. "The implant is inserted through a clear corneal, temporal wound," he says. "We often target the nasal quadrant and, if the anatomy allows, try to aim more for the 12 o'clock position. Placing the device in the temporal quadrant is not technically possible unless you alter your approach. We generally avoid placing blebs in the inferior quadrant—though this may change. Hence, one implant per patient is my general approach. A second device could be placed a few clock hours away in the same quadrant if the first becomes encapsulated and IOP is not optimally controlled, but the device has not been utilized in this way yet."

Dr. Panarelli offers surgical pearls that he's gathered from his firsthand experience implanting the device. "With this procedure, your first shot at delivering the device is your best one," he says. "When first learning to perform the procedure, I recommend doing a retrobulbar block or at least a peribulbar block. Minimizing patient movement and discomfort is extremely helpful in these cases. I also recommend visualizing the angle structures with a gonioprism after the injector is in position to get a feel for where the stent will go. The stent should be seated at or above the trabecular meshwork. Delivering the device too posteriorly will result in it being obstructed by the iris. I prefer to aim as anterior as possible, as I'm not worried about endothelial issues, given the small size of the

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implant and the fact that it barely protrudes into the anterior chamber if placed correctly.

"The most common issue is improper device placement, either leaving the implant too far outside the eye or too much inside the eye," Dr. Panarelli continues. "The stent is 6-mm long and should be positioned as follows: 2 mm of the stent in the subconjunctival space, 3 mm intrascleral and 1 mm in the anterior chamber. Delivering the device is a challenge at first as it is unlike any other procedure, but with practice it can become routine."

Because this procedure is unique and relatively new, Dr. Panarelli offers some tips on how to deal with common intra- or postop complications. "If too much of the implant is sitting outside of the eye, it's the result of exiting the sclera too anteriorly," he explains. "This is not ideal as the stent can end up taking a more curved course or become kinked. If the implant is too long inside the eye, it's likely because the device migrated back into the eye when the stent was being delivered. Gentle forward pressure is required during device delivery. Once the stent hydrates, it's rather difficult to grasp and advance farther outside the eye. Often, it must be removed and the procedure started again. Bleeding becomes an issue at this point, as there is often reflux blood at the site of the prior attempt. A cohesive viscoelastic should be used to tamponade that area and a new pass should be made in an adjacent area."

Because of the relatively recent approval of the device (November 2016), physician reimbursement is an important topic with the XEN. Dr. Panarelli says, "Currently, prior authorization needs to be obtained before XEN Gel Stent placement. Patients can pay out of pocket, and the claim can later be submitted for reimbursement. As with all new devices, this can be a challenging process at first."

Trabectome

Trabectome stands alone among the original MIGS procedures, as there is no device to implant. The procedure consists of the tip of the Trabectome removing a strip of the trabecular meshwork via microelectrocautery, increasing flow into the natural drainage system. This is done through the same corneal incision used in cataract surgery. Brian Francis, MD, MS, shares his experience and advice with this unique procedure.

As with the other surgeries, Dr. Francis emphasizes the importance of diligent patient selection in order to get the best outcomes. "The one advantage of the Trabectome is that it can be used as a combined procedure for cataracts and glaucoma treatment," he says. "We sometimes use it to treat severe glaucoma because it's all just based on target IOP. Anyone with open-angle glaucoma, primary steroid-induced, etc., can benefit from the procedure if we can hit their target IOP.

"Preoperative planning is essential to the success of the procedure, and this includes decent, consistent patient selection," Dr. Francis continues. "You just have to take the proper precautions prior to surgery. Intraoperatively, when I make my incision into the eye, I draw blood out so I can better see the target tissue. This tip basically applies to every MIGS. One of the most difficult parts of the Trabectome procedure is knowing when you're in. You have to make sure you have a good angle. Practice helps with this. You want to make sure you're not too deep, so sometimes you want to pull back to make sure you're not too far into the eye."

In terms of postop complications, Dr. Francis says that they're limited. "The thing with Trabectome is that you'll have some blood that can block your vision or mess with your angle, but that can be cleared up pretty quickly. Pressure spikes are also a possibility, but I don't really see them much after the number of procedures I've done. As with anything, you get better with practice. If anything does go wrong postop, I administer steroids and usually see a response within two weeks," he says. "That's about it. If the procedure is done correctly, there really is minimal risk of postop complications."

In a clinical study that evaluated the results of Trabectome for open-angle glaucoma, postop complications were minimal. Early IOP spikes, defined as IOPs >10 mmHg above baseline within one week after surgery, occurred in four eyes (4.9 percent). Hyphema was observed in 19 eyes (23.3 percent). Hyphema was minimal and disappeared without any special management one to 10 days after surgery.[2]

Dr. Francis describes the reimbursement for Trabectome as more than satisfactory. "It's good," he says. "It's been steady ever since it's had a regular CPT code. There are actually two reimbursement codes that can be used: The trabeculectomy code or the gonioscopy code. Surgeons just use whichever one they prefer. I think the reimbursement is slightly different, but it's consistent."

The biggest issue with the procedure is purchasing the equipment, says Dr. Francis. "When I talk to other surgeons, the biggest barrier with Trabectome is startup costs," he says. "Typically, the surgery center will prefer other methods, so it's a pain to try to convince them otherwise. Hopefully there will be programs soon that minimize startup costs."

The Kahook Dual Blade

In terms of newer MIGS devices, the single-use Kahook Dual Blade appeals to surgeons because of its flexibility in treating different patient types. The KDB procedure consists

of passing the blade through a clear corneal incision and using it to make two parallel incisions in the TM and the inner wall of Schlemm's canal.

Malik Kahook, MD, the creator of the device, gives his advice on how to get the best results. Again, it all begins with patient selection, he says. "A typical patient is one who has co-existing cataracts, with mild to moderate glaucoma," he explains. "The goal is to decrease dependence on topical medications as well as to lower intraocular pressure. Another group of patients includes those who are already pseudophakic and can benefit from a reduction in both medications and IOP. Patients with chronic angle closure glaucoma, pseudoexfoliation and pigmentary glaucoma seem to do particularly well with KDB treatment."

Dr. Kahook provides some intraoperative tips. "Learning how to do intraoperative gonioscopy is key," he says. "For surgeons who are doing *ab interno* angle procedures already, picking up KDB will be a smooth transition with only minor differences compared to other angle-based approaches. I always recommend that surgeons practice goniocopy intraoperatively on five to 10 cases before attempting their first angle procedures. I recommend using a cohesive viscoelastic to deepen the angle and maintain the anterior chamber. The surgeon should be careful not to press too hard with the lens since this causes corneal striae and will obstruct your view.

"Other pearls for use include positioning the head of the device against the anterior wall of the canal without lifting up, which allows the ramp on the KDB to do the job of lifting up the trabecular meshwork so the blades create parallel incisions," he continues. "At the end of the case, the surgeon should hydrate

(Continued on page 59)


High-tech Mythbusting: Glaucoma and the Macula

As new technology reveals more about the connection between structure and function, many old ideas are falling by the wayside.

Jeffrey M. Liebmann, MD, New York City

Although our understanding of glaucoma increases every year, there are still a number of misconceptions about the disease. Two of the most important have to do with the macula's role in glaucomatous damage and the correlation between structure and function.

Generally, ophthalmologists treating glaucoma haven't paid much attention to the macula because it's been widely accepted that glaucoma primarily affects an individual's peripheral vision. That myth was perpetuated in the past because Goldmann perimetry doesn't allow us to detect small amounts of central vision loss; the six-degree grid spacing of most automated perimetry algorithms doesn't adequately sample the central 10 degrees of the visual field. In addition, prior to the advent of optical coherence tomography we had no way to analyze the condition of the macular structure. So, ophthalmologists focused on the topography of the optic nerve and the central 30 degrees of the visual field.

We now have technologies such as spectral-domain and swept-source OCT that allow us to look at both the circumpapillary region and macular anatomy with ever-increasing resolution. As a result, we can now demonstrate the appearance of structural alterations in regions of the macula in glaucoma patients, localized to retinal ganglion cells and their axons, and the connections to those cells. Problems such as disc hemorrhages have been visible in photographs all along, but our current technology is now revealing the significance of these phenomena and how they correlate to macular damage.

Another side effect of limited technology has been the belief that damage to the central visual field (and the corresponding retinal ganglion cells) only occurs late in the disease. Today's technology has revealed that some macular defects occur very early in the disease process. Furthermore, they can significantly undercut the patient's quality of life.

A third widespread idea is that there's a disconnect between structural damage and functional damage. However, with our increasing ability to image the retina in greater detail, it's becoming clear that there is a very direct, precise relationship between glaucomatous structural damage and functional impairment throughout the retina, especially in the macula.

A fourth belief that's been widely accepted is that our imaging devices stop being useful once glaucomatous disease becomes advanced. But as our technology becomes more sensitive, we're finding out that this may not be the case.

Here, I'd like to share some of what we've learned about these issues, to encourage those of us who are treating glaucoma to take full advantage of the technologies now at our disposal and to pay more attention to what's occurring in the macular region.

The Anatomy of Central Vision

The idea that central loss is occurring in glaucoma isn't really new; even 50 years ago the literature contained references to central loss.[1] It was simply more difficult to measure and evaluate. Ironically, central loss is what's important to the patient. When patients walk in the door, they don't say that their nasal step is bothering them. They say they're having difficulty reading, or they have

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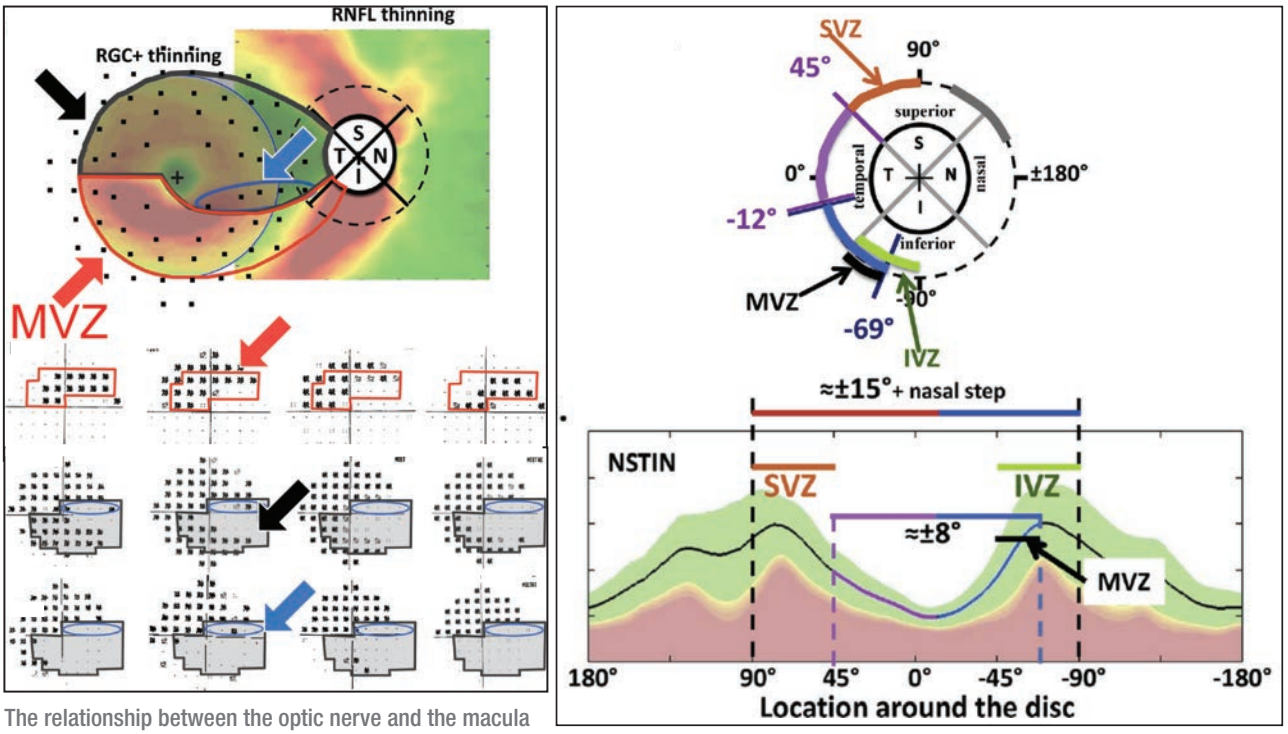


The relationship between the optic nerve and the macula has been well described by Don Hood, PhD. Cells leaving the optic nerve travel to different parts of the retina; damage to those cells that pass through the "macular vulnerability zone"—which includes the segment between 295 degrees and 322 degrees on the inferior optic disc—results in a paracentral visual field defect. *(See the red-outlined area in the diagram, above left.)* The MVZ is one part of the inferior vulnerability zone, encompassing the inferotemporal section of the optic nerve. *(Above, right)* This is matched by a superior vulnerability zone that lies above the maculopapular bundle. These nerves are more susceptible to damage than the maculopapular bundle, and they're responsible for damage seen outside the central 10 degrees at the superior and inferior poles, such as nasal steps, arcuate scotomas and peripheral field loss. (For more information about these correlations, see references 7-9. Diagrams reprinted with permission.)

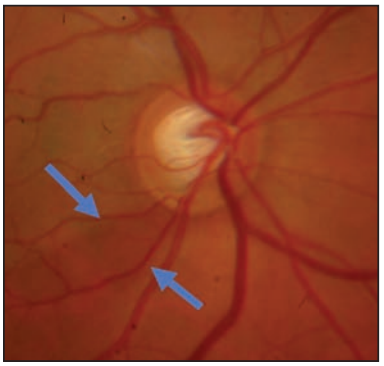
decreased contrast sensitivity—visual functions that are primarily related to macular function.[2,3] They may be having trouble driving, or may be falling because of impaired vision.[4-6] In fact, most patients don't complain about peripheral loss unless it's severe and bilateral. At that point the disease is very advanced.

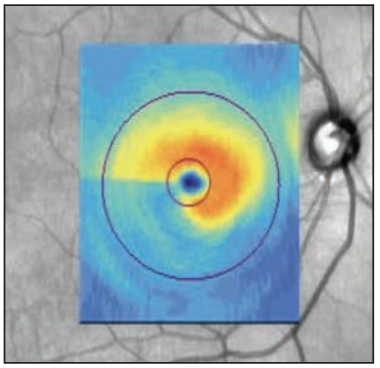
Because of the prevailing idea that glaucomatous damage is peripheral, we tend to pay minimal attention to the central visual field and central visual function. With our current technology and understanding, that may be a disservice to our patients.

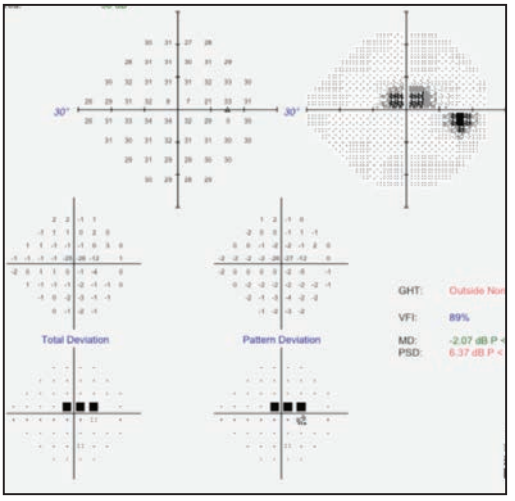
To understand how glaucomatous damage affects vision, it helps to think about macular anatomy. The retinal ganglion cell axons become the retinal nerve fiber layer, which converges on the disk and forms the optic nerve. So when you use OCT to perform a circumpapillary scan, you're measuring the thickness of the retinal nerve fiber layer. The inner plexiform layer, or IPL, is formed by the connections between the retinal ganglion cells and the inner nuclear layer below it. In the macula, the retinal ganglion cells and the inner plexiform layer are the structural elements that are damaged and thin out; neither the inner nuclear layer itself nor the receptor layer are damaged. So when we measure macular damage in glaucoma, the retinal ganglion cell layer and the inner plexiform layer are typically what we're measuring.

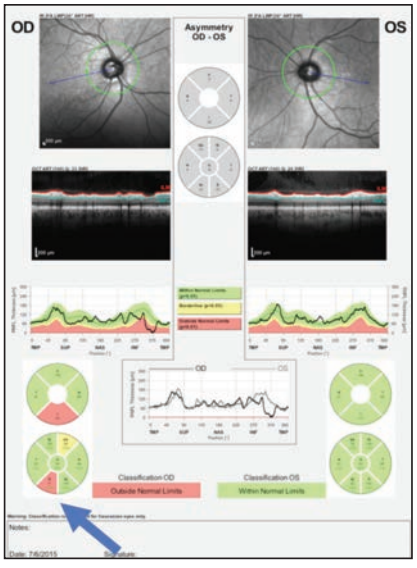
A note regarding terminology: Although we're primarily interested in the retinal ganglion cells, it's very difficult to separate the retinal ganglion cell layer and the inner plexiform layer with our current technology, so we usually treat them as one layer. We refer to this composite layer as the "retinal ganglion cell-plus," or sometimes simply call it the ganglion cell complex.

The retinal nerve fiber layer tends to be thicker near the disc because all the fibers are converging there. In contrast, when you look at the macula, there's not much retinal nerve fiber layer. The main focus there is on retinal ganglion cells and the ganglion cell complex. (Note that in the foveal depression, where we have the most photoreceptors and our most sensitive vision, there are no ganglion cells at all. The cell bodies that process the









A case history illustrating the correlation between structure and function. Above and left: Disc photo, visual field and OCTs of the optic nerve and macula all confirm inferior macular damage, which correlates with the superior field loss. Facing page: Three months later, the patient has a disc hemorrhage at the same location, indicating ongoing damage.

visual information are actually all displaced away from the center a little bit, to allow the light to come through perfectly clearly.)

Vulnerability Zones

The structure-function relationship of glaucomatous damage to the macula has been described in detail by Don Hood, PhD, of Columbia University.[7-9] The most susceptible region of the optic disc has been termed the Hood macular vulnerability zone. It's about 27 degrees wide and lies between 295 degrees and 322 degrees on the inferior optic disc. When damage occurs along the cells' path through that region, the result is a paracentral visual field deficit. This is well-illustrated in the images on p. 43.

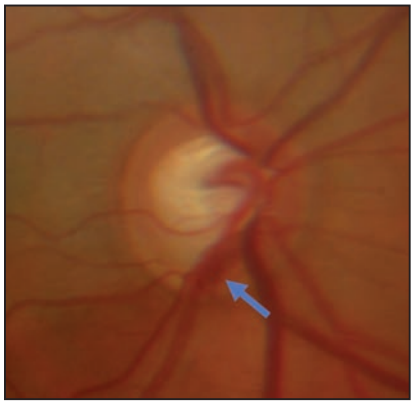
This macular vulnerability zone corresponds to the inferotemporal location on the nerve and is the part that's often damaged in glaucoma. This correlation has been confirmed by data from the ADAGES study, which found that an inferotemporal disc hemorrhage is associated with a central visual field deficit. If you see a disc hemorrhage at that location, you need to be concerned about the central field and do a 10-2 visual field test.

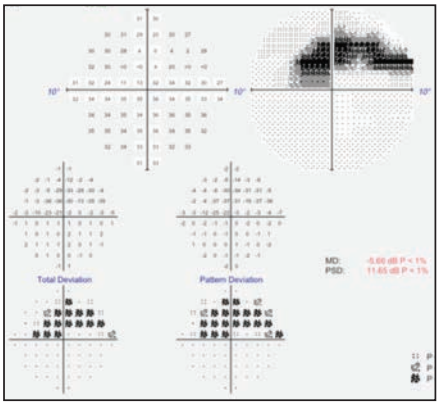
Fortunately, not all parts of the macula are equally vulnerable to glaucomatous damage. The retinal ganglion cells and their axons that serve in the superior half of the macula pass through the temporal region of the optic nerve. This region, called the maculopapular bundle, is resistant to damage. *(See diagrams, p. 43)* As a result, the part of the macula enervated by those nerves tends to be the last to lose vision. That's a blessing for those with advanced glaucoma, because they can at least retain central vision until very late in the disease.

It's worth noting that the macular vulnerability zone is just a part of what's called the inferior vulnerability zone, encompassing a broader swath of optic nerve rim tissue comprising the inferotemporal section of the optic nerve. This is matched by a superior vulnerability zone that lies above the maculopapular bundle. The superior segment nerves, along with the group of inferior segment nerves that don't end up in the macula, are more susceptible to damage than the maculopapular bundle; they are responsible for damage seen outside the central 10 degrees at the superior and inferior poles, such as nasal steps, arcuate scotomas and peripheral field loss. Despite the fact that these types of damage are often detected first, central visual loss is probably occurring simultaneously. It may even occur first. It's simply been more difficult to detect.

Structure and Function

The most important thing to understand is that there really is a direct relationship between structure and function. Once we account for retinal ganglion cell displacement, there's a high correlation between retinal nerve fiber layer thickness, ganglion cell complex thickness and visual field deficits.[10] I'm sure that if our tools were sensitive enough, the





loss of a single ganglion cell would be detected as a loss in function. But when we check function with our current technology (the 24-2 strategy with the automated perimeter), that correlation may not be obvious; it might appear that the visual field is still normal, despite the loss of many cells. What we find will depend largely on our technologies and how we use them, but the structure-function relationship has to be intact. Otherwise, everything we know about glaucoma makes no sense.

Consider the example shown on these two pages—a young person who had an abnormality of the disc. All of the structural and functional tests correlate beautifully. The disc photo shows inferotemporal disc damage in the right eye (facing page, between the two blue arrows), a small central paracentral scotoma in the center of the field. OCT imaging shows a nerve fiber layer defect at that location. The OCT of the macular region confirms the problem; the color map should be orange/brown all around the fovea, but you can see that it's cut off and truncated, leaving a comma-like shape. That's inferior macular damage, which correlates to the superior field loss seen in the visual field test. Furthermore, three months later (above) the patient had a disc hemorrhage at that location (blue arrow), telling us that the damage is ongoing. All of this data taken together shows a perfect structure-function correlation between the optic nerve, the nerve fiber layer defect, the macular damage and the visual field loss on a 24-2 and a 10-2.

The "Floor Effect"

Another way in which the seeming structure-function disconnect has affected our use of technology is via the belief that structural damage always has a "floor effect." This simply means that at some point, the tissue whose thickness we're measuring bottoms out; it can't get any thinner, so measuring it after that won't tell us anything. For example, once the nerve fiber layer gets to 40 or 50 µm thick, it's very hard to detect further change.

However, the better our tools, the more we're finding that this isn't the case. There's evidence that this type of structural measurement may still be useful; the key is that while overall thickness may have bottomed out, the thickness in specific key locations may still be changing, even in advanced disease. (Monitoring a specific, small area rather than the entire eye is called the "region of interest" approach.)

For example, the average retinal nerve fiber layer thickness may appear to be normal. If the patient loses a small amount of nerve fiber layer thickness that's very localized, and you're just checking the overall thickness, you won't note much change. The part that's changing is lost in the averaging process. However, if you look just at the damaged area, you might find very rapid progression.

The same is true for visual fields. If the patient has a normal field but then converts to an abnormal field, only two or three of the points may have changed. The mean deviation doesn't change that much. But the areas of interest with localized damage (i.e., the few points that are changing) could be changing at -5 or -6 dB per year.

Of course, we're just figuring out how to use this approach because our technology is advancing so quickly. But the bottom line is that we need to look at regions of interest, not just overall averages of change. The ongoing loss of function is almost certainly accompanied by an ongoing loss of structure; we just haven't known how to detect it.

Helping Your Patients

Given these insights about how glaucomatous damage may be occurring and may affect the macula, here are a few things you can do to help your patients:

• ***Ask patients about problems they may be having that relate to loss of central vision.*** Don't assume the periphery is the only area needing your attention. Issues associated with central vision deficits may well be associated with the patient's glaucoma and indicative of damage that needs to be addressed.

• ***If you see a sign of trouble, test the macular region with the 10-2 test.*** In order to test the function of central vision, it's important not to rely on the 24-2 visual field test. In that test, the test points are pretty widely spaced (six-degree separation), resulting in very little information about central vision. In a 10-2 visual field test, the test points are much

closer together—spaced about every two degrees. That results in a much more effective test of functional central vision.

• ***Be alert for signs of trouble in the areas known to be most vulnerable to glaucomatous damage.*** Now that the structural layout of the ganglion cell complex is better understood, be extra vigilant for signs of damage in the vulnerable zones around the optic nerve.

• ***If your patient's glaucoma is progressing, pay close attention to any change in areas already known to be problematic.*** The evidence suggests that change in areas already subject to trouble is likely to be greater than the overall, average change, making this a more effective warning sign that progression is occurring. This is especially true in advanced glaucoma, where significant damage has already occurred.

• ***Use all of the technologies available to you.*** As noted above, our evolving technologies are making it clear that any seeming structure-function disconnect may be an artifact of our technological limitations—limitations that are diminishing every year. So use all the technologies available to you to monitor your patients. REVIEW

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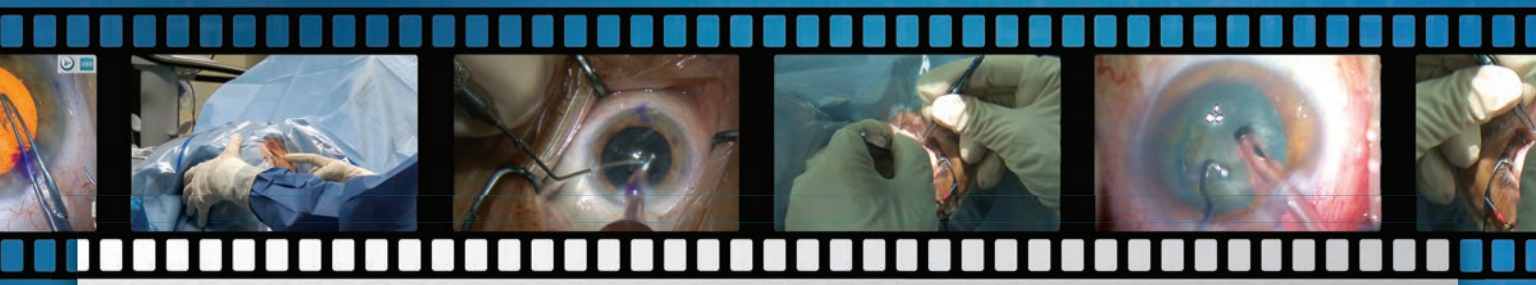

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Richard J. Mackool, MD

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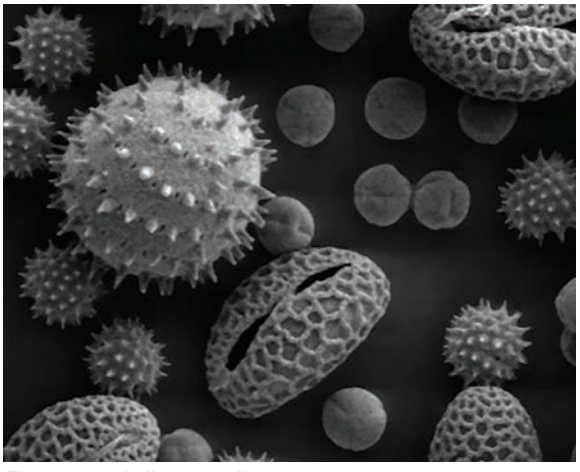
Reaching Beyond the Low-Hanging Fruit

Just because the easiest routes to treating allergy have been explored doesn't mean we can't do better.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Paul J. Gomes, and David A. Hollander, MD, MBA
Andover, Mass.

Those in the business of drug discovery would probably tell you that the low-hanging fruit in the allergy therapeutic space has been picked. Antihistamines, mast cell stabilizers and short courses of topical steroids[1] are treatments with good efficacy and reasonable safety, and they provide relief for most of our patients with ocular allergies. Why reach for the more difficult-to-develop treatments? The corollary to the fruit apothegm is that the high, hard-to-reach fruit is often the best fruit on the tree. Similarly, finding treatments to address the remaining unmet need represents a prospect of transformative therapy; in ocular allergy, this need takes the form of the patients with more severe conditions such as vernal or atopic keratoconjunctivitis, or the patients with chronic perennial allergies that respond poorly to existing treatments. These are a minority of the total allergy patient population, but a sizable group nonetheless. The pace of development in the ocular allergy space may have slowed, but there is still important progress to be made. This month we survey some of the directions in which these efforts are heading.



The seasonal allergen pollen.

Identifying Targets

In immune reactions such as allergic conjunctivitis, there is a series of cellular events, including sensitization to the allergen, presentation by dendritic cells and priming of naïve T cells that collectively lead to production of IgE-producing B cells.[2] Upon subsequent exposure, the complex of antigen, IgE and immunoglobulin receptors will cross-link on conjunctival mast cells, causing degranulation and release of histamine and other pro-inflammatory factors. In the continued presence of antigen, this immediate hypersensitivity can lead to a late-phase response (typically hours later) in which other immune cells, particularly neutrophils and basophils, are recruited to infiltrate into the conjunctiva. This T helper-2-type response is an inappropriate activation of the immune system. The process is not a single event; rather, it is a signaling cascade that presents multiple potential targets. Although there is a wealth of basic science that identifies possible points of therapeutic intervention, significant work remains before isolating the key step for disease modification.

One of the most attractive sites for new drug targeting is spleen tyrosine kinase (Syk).[3] Syk-catalyzed phosphorylation mediates interactions between the Fcε receptors and their downstream targets, and Syk is one

of several kinases implicated in this allergic cascade. *(See the May 2013 Therapeutic Topics for details.)* Syk inhibitors have been touted as potential therapies for leukemias and lymphomas, for autoimmune and allergic asthma conditions, and for allergies.[4] There are a number of small molecule Syk-targeted compounds in clinical-stage testing, and trials involving allergic disorders are likely in the near future.

Like Syk, other kinase inhibitors have the potential to be useful therapies for ocular allergy. A recently published study found the long sought after bridge between mast cells and asthma by demonstrating the positive effects of imatinib (Gleevec, Novartis), a kinase inhibitor currently approved for treatment of chronic myeloid leukemias and stromal tumors.[5-7] This drug inhibits multiple kinases, including a key mast cell growth regulatory kinase called KIT; in patients with refractory asthma, it increased airway hyper-responsiveness and reduced mast cell numbers. While the adverse effects of imatinib may preclude its use for AC, this does provide a clear proof of principle in the use of KIT inhibition as a tool to address mast cell-mediated disorders.

Another kinase in the crosshairs is IkK-β, a component in the NFκB gene regulatory pathway.[8] This pathway is responsible for upregulation of pro-inflammatory signaling molecules. And under resting conditions it's kept silent by the action of the Ik-β, a protein that stabilizes the inactive complex. When phosphorylated by IkK-β, it is released from the complex, which allows activation of its gene-regulating function. Inhibitors of this kinase share some of the functional transcriptional suppression action elicited by corticosteroids. Experimental compounds such as SAR113945 (Sanofi) have been tested as treatments for osteoarthritis,[9] and similar compounds may have a role in chronic allergy therapy.

We can't leave a discussion of repurposing kinase inhibitors without mentioning two important kinase families, the ROCK kinases and the MAP kinases. Both are targets of therapies in a host of different disorders, from glaucoma to various neoplasias. Compounds focused on these molecular targets are best suited to an empirical assessment of efficacy in ocular allergy and inflammation. The benefit of the eye as a target is the simplicity of access and of rapid and reliable assessment of response.

On a different front, efforts to unravel the mechanisms of action for several compounds derived from natural products used as allergy treatments (such as flavonoids, stilbenes and curcuminoids)[10] have narrowed the focus to a common mast cell stabilization effect, as demonstrated by *in vitro* studies in basophilic cell lines.[11] Given the apparently common mechanism in several disparate herbal preparations, interest in mast cell stabilizers may be on the horizon.

The State of Immunotherapy

One of the most anticipated therapeutic arrivals in ocular allergy treatments of late came in 2013 and 2014,

A Looming Obstacle to Drug Development?

This month's discussion of allergy drug development reminds us of a subject that's been on our mind of late. Prescription benefit systems developed decades ago have evolved from aiding cost-containment to selecting winners and losers. What used to be about choosing the most appropriate therapy has become a process of placing an order from a very limited menu. The recent uproar about drug costs and rebates to PBMs has led to public discussion about how costs are set, and the role of the pharmacy benefit managers in both cost and access. Access is what particularly concerns us.

As an example, of the prescription ocular antihistamines currently approved for b.i.d. or q.d. dosing in the United States (about 10 in all, including generics), only two chemical entities are available from one of the major formularies. Similarly, prostaglandin eye drops are available in multiple formulations, but only two of these are available (i.e., reimbursable) from that same PBM. Like many classes of drugs, ophthalmic anti-allergic medications or medications for glaucoma have similar, class-based therapeutic indications. What experience has taught us, however, is that each patient reacts differently to a given medication. Although the majority of patients experience significant therapeutic benefit from most of the available agents in a given class, there are invariably differences in response among patients. One treatment option for each condition is not an effective strategy. It seems that formularies have evolved into a system that operates counter to this concept and determines which of the agents with a given indication will be blessed to be included on formularies' lists. What if the approved therapy doesn't work for you? If you want your brand, then you pay 10 times as much after calling a dozen pharmacies to find one that carries the product you're looking for.

What especially concerns us is that these principles are being applied to drugs for more serious indications: Most PBMs are already dictating the types of insulin they will provide diabetics, even though most patients have training, pumps, or both designed for one formulation. If you're diabetic, you'd better hope your coverage includes your insulin; often, it does not. And is it reasonable for the PBM to decide that you can get coverage for Lucentis but not Eylea? Isn't that a decision for the physician and patient? Furthermore, how does this system ultimately impact the future of drug development, when it seems possible that, after working years to gain regulatory approval for your therapeutic, you find that the PBM has decided not to include it in the formulary of reimbursable drugs? It appears that a system that began as an attempt to control drug costs has morphed into one in which winners and losers are selected, and many potentially useful treatments may never get a chance to demonstrate their benefit.

—MBA

with approvals of sublingual timothy grass antigen extracts as a desensitizing approach to seasonal allergies.[12,13] These approvals received a first-ever FDA indication for "allergic rhinitis with or without conjunctivitis," opening the door to future treatments for rhino-conjunctivitis. This treatment approach, in which continuous exposure to low-level allergen leads to a switch from the pro-inflammatory Th2 to the anti-inflammatory Th1 profile, is designed to reduce and, ultimately, extinguish the allergen sensitization. Although this desensitization process isn't completely understood, increases in IL-10, TGF-P and INF-γ are thought to promote a conversion from IgE to IgG antibody production, a suppression of inflammatory leukocytes and an attenuation of subsequent responses to allergen exposure.

After a little less than three years on the market, it appears that primary competition for these new therapies wasn't oral or topical anti-allergic medications, but the injection protocols allergists have been using for many years to achieve the same desensitized endpoint. Sales of Grastek (Merck) and Oralair (Stallergenes) have been much less than anticipated, and Merck returned product marketing rights to its development partner, ALK-Abello, in July 2016. Despite this, another Merck/ALK-Abello immunotherapy targeted against the perennial allergen the dust mite[14] was approved by the FDA in March 2017. It will be interesting to see how those with perennial allergies respond to the availability of this new therapy, and whether long-term efficacy can generate a market that has not been seen with the seasonal allergic immunotherapy treatments.

This is where we stand in 2017: a list of potential compounds with intriguing anti-inflammatory effects highlighted by a long list of kinase inhibitors with the potential for successful repurposing. Of course there are other compounds at earlier stages of development that constitute the future of allergy therapeutic progress, where a steady flow of test compounds will be gauged for their ability to meet the high bar that has been established. There is still much progress to make in refining and optimizing drugs, but we have the benefit of a solid base of therapeutic options that makes it possible to reach for the very best of new treatments. REVIEW

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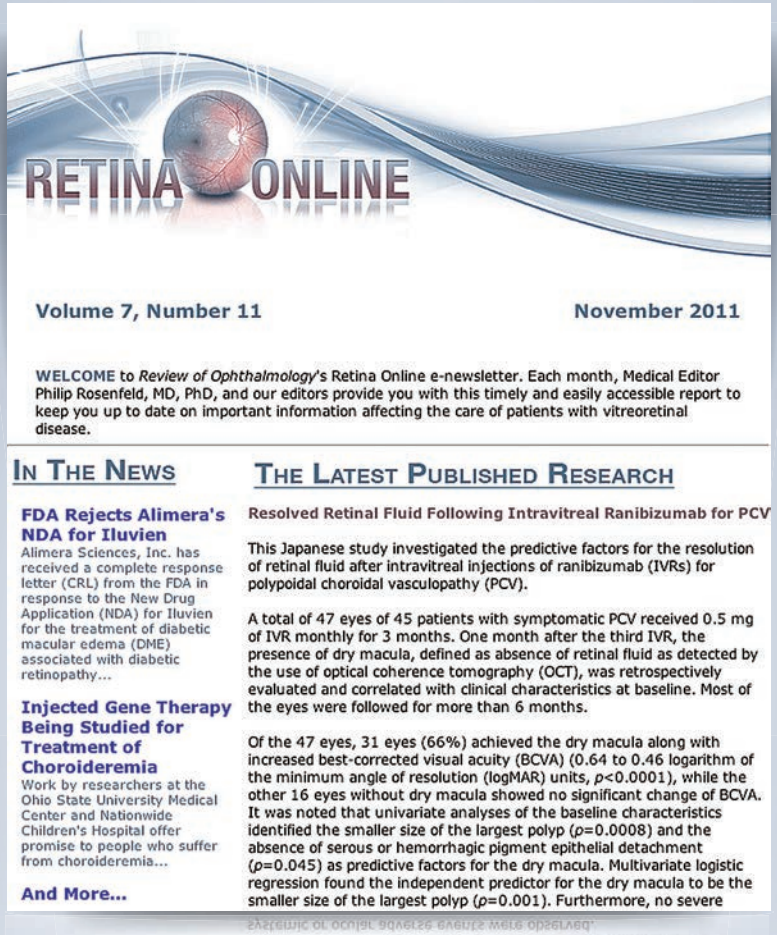

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Volume 7, Number 11 November 2011

WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

IN THE NEWS

FDA Rejects Alimera's NDA for Iluvien
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THE LATEST PUBLISHED RESEARCH

Resolved Retinal Fluid Following Intravitreal Ranibizumab for PCV

This Japanese study investigated the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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Retinal Prostheses—Now and in the Future

A discussion of the unique strategies used by the major retinal prostheses initiatives and their current results.

Derrick L. Cheng, David A. Borton, and Paul B. Greenberg, MD, Providence, R.I.

The goals of retinal and visual prosthetic initiatives have evolved significantly over the past half-century. Initially, researchers aimed to produce visual percepts, eliciting phosphenes through stimulation of the occipital cortex. These devices contained few electrodes and weren't designed for chronic human implantation, but led to the development of early prosthesis prototypes. Contemporary prosthetic approaches now target various points of the visual pathway, using more advanced technology to improve visual acuity and biocompatibility. This review describes the history of visual prosthesis development, introduces current approaches to retinal stimulation around the world and highlights directions for future research.

The Need for Prostheses

There are a variety of diseases that target the visual pathway, with retinitis pigmentosa and age-related macular degeneration being two of the leading causes of photodegenerative blindness in the United States.[1]

Retinitis pigmentosa is a complex genetic disease typically characterized by retinal hyperpigmentation and photoreceptor death. Retinitis pigmentosa initially affects rod cells and low-contrast peripheral vision, while sparing high-acuity central vision. In more severe forms of the disease, however, visual acuity can fall to 20/200 (25 percent of cases) or zero light sensitivity (0.5 percent of cases) due to damage to macular cones.[2,3]

While AMD is also characterized by photoreceptor death, it typically results in the progressive loss of central visual acuity due to cone cell damage. Age-related macular degeneration is the leading cause of progressive blindness in the elderly.

Though anti-vascular endothelial growth factor treatments, as well as photodynamic therapy, have helped minimize disease progression in AMD,[4,5] there are few available options for restoration of functional eyesight in patients who have significant photoreceptor loss. Several approaches, however, including retinal/visual prosthesis implantation, optogenetic stimulation and stem cell therapy, are currently being developed to restore some level of functional vision in patients suffering from these conditions.

Early Visual Prostheses

The earliest forays into visual stimulation began in 1918 with the work of Lowenstein and Borchardt, who elicited flickering sensations of light through occipital stimulation in a projectile-wound patient.[6] Similar results were obtained by Krause in 1928 and Foerster in 1929, who conducted further stimulation studies in projectile-wound patients. Their experiments produced phosphenes of light in predictable, retinotopic patterns in blind or hemianopic patients and suggested that future prototypes could potentially allow patients to avoid obstacles when walking, and to read at speeds comparable to sighted individuals.[6]

These findings led to the development of early prostheses that were tested in humans by Brindley and Lewin in 1968, who examined retinotopy, phosphene threshold, pulse duration and frequency requirements in a bilateral glaucoma patient using an 80-electrode platinum array.[6,7] Later prostheses developed by Dobelle (1974) and Normann (1989) expanded on this concept and were able

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Table 1: Engineering Characteristics and Current Status of Major Retinal Prosthesis Initiatives

Device	Description
Argus II[11,18] Second Sight (Sylmar, Calif.)	• glasses-mounted camera with inductive power and data transfer to external electronics unit strapped around the eye • 60-electrode array implanted into the **epiretinal** space • currently the only FDA (2013)- and CE (2011)-approved retinal prosthesis
IMI GmBH Learning Prosthesis[19,20] Intelligent Medical Implants (Bonn, Germany)	• uses a learning encoder to analyze and account for natural retinal processing • 49-electrode array implanted in the **epiretinal** space • completed safety and charge threshold trials for temporary implantation in humans • acquired by Pixium (now "Pixium IRIS"); undergoing trials for a 150-electrode device
Epi-RET3 Intraocular Prosthesis[21,22] Aachen University (Aachen, Germany)	• uses an artificial lens implanted in the anterior chamber of the eye (lens capsule); responds to extraocular movements • 25-electrode array implanted in the **epiretinal** space • completed clinical trials in six patients implanted over 28 days
Artificial Silicon Retina[23,24] Optobionics (Chicago)	• uses light-powered photodiodes without an external power source or other electronics • 5,000 microelectrode-tipped photodiodes implanted in the **subretinal** space • completed multicenter clinical trial but was unable to provide adequate stimulation current for vision restoration
Alpha-IMS[25,26] University of Tübingen (Tübingen, Germany)	• uses a microphotodiode array with an external power amplifier • 1,500 microphotodiodes and microelectrodes implanted in the **subretinal** space • currently conducting a long-term multicenter clinical trial (started in 2010) • CE-approved; has attained the highest restored visual acuity to date (20/549)
Boston Retinal Implant[14,27] Boston Retinal Implant Project (Boston)	• glasses-mounted camera with inductive power and data transfer to external electronics unit strapped around the eye • 100-electrode array implanted in the **subretinal** space • currently undergoing preclinical trials in nonhuman primates; recently completed trials in Yucatan minipigs
Photovoltaic Retinal Prosthesis[28-30] Stanford University (Stanford, Calif.)	• uses photovoltaic cells and an infrared headset to wirelessly stimulate the retina • 143 hexagonal pixel cells (three microphotodiodes each) implanted in the **subretinal** space • acquired by Pixium ("Pixium Prima"); currently conducting preclinical testing in mice
Liquid Crystal Polymer Prosthesis[31] Seoul National University (Seoul, Korea)	• uses liquid-crystal polymer to provide a lightweight and durable alternative to traditional electrode substrate and casing materials • 16-electrode array implanted in the **subretinal** space • currently undergoing preclinical trials in rabbits
Bionic Vision Australia[32] University of Melbourne	• developing a **suprachoroidal** and an **epiretinal** "Wide View" stimulator • 33-electrode array implanted in the **suprachoroidal** space (pilot studies in three patients) • 99-electrode array implanted in the **epiretinal** space (early development)
NIDEK Visual Prosthesis[33,34] NIDEK (Gamagori, Japan)	• uses 3D electrodes instead of traditional contact microelectrodes • 49-electrode array implanted in the **suprachoroidal** space • completed pilot studies of two patients implanted over four weeks in 2011

to test high-density electrode arrays in sighted and blind patients.[8-10]

Applications Using the Retina

While the occipital lobe has the advantage of being a large, accessible target for stimulation, a great deal of processing occurs between the retina and the visual cortex. Hence, recent focus has shifted towards points in the visual pathway such as the retina, optic nerve and lateral geniculate nucleus of the thalamus. The development of retinal prosthetics has seen remarkable growth over the past 20 years due to surgical accessibility, technological advances driven by the semiconductor industry and the lack of complex processing in the retina compared to later points in the visual pathway.

A retinal prosthesis is often composed of three key components *(See Figure 1)*: an image capturing unit; a video-processing unit; and a microelectrode array. The image-capturing unit, often a glasses-mounted video

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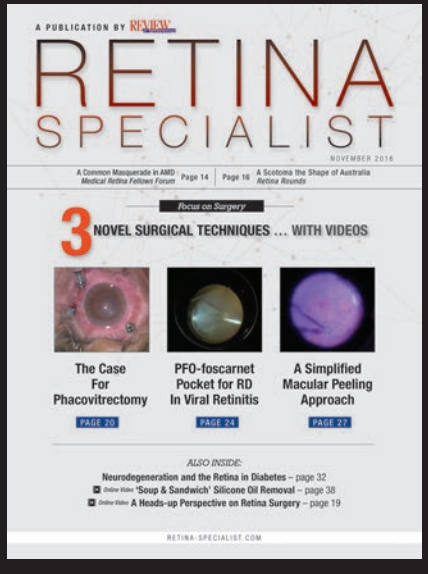

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camera or microphotodiode array, takes light information and transforms it into electrical information much as photoreceptors do. Information is transmitted from the camera to a video-processing unit, often worn on the patient's belt, which compresses and simplifies complex image information into points of electrical stimulation. The VPU transmits this information via induction, light or wire to electronics implanted in and around the eye, which receive the encoded stimulation data and directly activate the retina.

Retinal approaches are often organized based on stimulation target. *(See Figure 2)* Microelectrode arrays are typically implanted into the subretinal space between the retinal pigment epithelium and bipolar cells, the epiretinal space between the vitreous humor and retinal surface, or the suprachoroidal space just beneath the posterior sclera. Each approach has potential benefits and drawbacks.

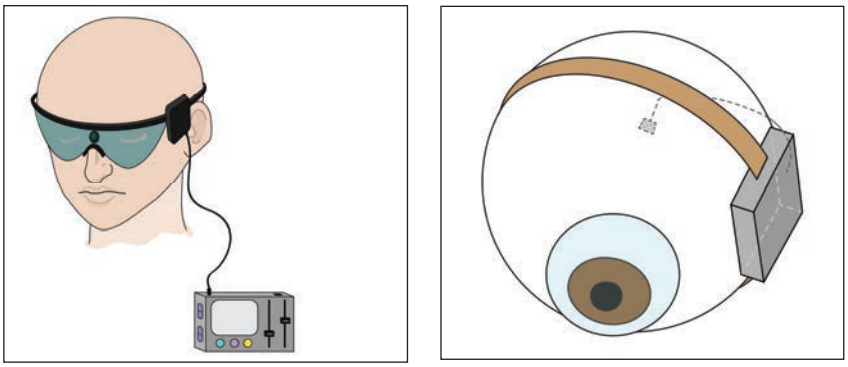

Figure 1. Typical components of a retinal prosthesis: an image-capturing unit; a video-processing unit; an external transmitter; an implanted electronics case; and a microelectrode array. Other alternative designs include the use of infrared power and data transfer, microphotodiode arrays for light capture and implantation of the electronics case into the lens capsule.

Epiretinal stimulation, for example, allows for heat dissipation through the vitreous and implantation of larger arrays through a pars plana vitrectomy; however, it also requires stabilization with a retinal tack which may result in array dislodgement or gliosis.[11-13] Since it directly stimulates the retinal ganglion cells, this approach may also

Table 2: Methods for Alternative Stimulation of the Visual Pathway

Approach/Target	Description
Optic nerve stimulation	Optic nerve stimulation uses cuff electrodes or penetrating electrodes wrapped around the optic nerve to take advantage of the high accessibility to the axon fibers and the entire visual field. However, it's difficult to target select fibers for visuotopic stimulation or develop arrays with high electrode densities.
Lateral geniculate nucleus stimulation	The LGN is the first point at which color, motion and brightness information are aggregated, allowing for potential restoration of detailed color vision. However, the thalamus is bilateral, deep and small, and may prove to be a difficult target for synchronized stimulation with a high number of electrodes.
Cortical stimulation	The visual cortex, located in the occipital lobe, is a large target that may allow for a high number of electrodes to be implanted through relatively well-understood procedures. Stimulation is also able to target diseases affecting any area of the pre-cortical visual pathway. However, this approach requires an advanced understanding of retinal, thalamic and other extracortical physiology and processing that occurs prior to V1.
Optogenetic treatment	Optogenetics revolves around the use of viral vectors and opsins to photosensitize retinal neurons. This approach requires no implanted electronics and is currently being tested by a variety of groups. The only active clinical trial of optogenetics for vision loss involves transfection of channelrhodopsin-2 into RGCs by RetroSense Therapeutics.
Neurotransmitter titration	Neurotransmitter-based stimulation involves the titrated release of neurotransmitters directly onto the retinal surface using microfluidics. Like optogenetics, this approach aims to provide more natural stimulation and is able to selectively target neuron soma.

require more advanced image processing.[13]

In contrast, subretinal stimulation directly targets the bipolar neurons and doesn't use tack fixation, but instead requires the use of trans-scleral cables and specialized surgery involving injection of a subretinal saline bleb.[12-14] Though suprachoroidal approaches require a less-invasive surgical procedure, they result in a greater distance between the electrode array and retinal tissue, which may limit the potential for high-acuity restoration.[13]

Our group recently reviewed and conducted an engineering analysis of 10 retinal prosthesis initiatives.[15] *(See Table 1)* Of these, four have recently completed human trials (Argus II, IMI GmBH, Epi-Ret3 and ASR), three are undergoing single- or multicenter human trials (Alpha-IMS, BVA and Nidek) and three are undergoing preclinical animal studies (BRIP, Photovoltaic and LCP). Prostheses typically use microphotodiodes or external glasses-mounted cameras for image capture, light-based or inductive power and data transfer, and a microelectrode array composed of a polymer substrate and platinum or iridium oxide electrodes.[1,11,16,17] Only the Argus II has been approved by the Food and Drug Administration, and both the Argus II and the Alpha-IMS have been approved for commercial use in Europe. The Alpha-IMS has attained the highest visual acuity to date using a Landolt-C test (20/546), and is the only device currently undergoing a multicenter clinical trial.[17]

Retinal prostheses have demonstrated significant progress in improving visual acuity and activities of daily living in blind patients. Several initiatives reported that patients were able to navigate their surroundings, identify objects and read large letters using implants or simulations.[25,35,36] However, retinal stimulation requires surviving bipolar and ganglion cell targets within the retina. Though photodegenerative diseases like RP and AMD leave the inner layers of the retina relatively intact, other common conditions such as glaucoma, ocular trauma and optic neuritis damage the retina or optic nerve, precluding the use of retinal prosthetics.[12] To this end, several initiatives *(shown in Table 2)* are also conducting research on alternative targets for electrical stimulation (visual cortex, thalamus and optic nerve) and non-electrical stimulation (optogenetic and neurotransmitter titration).

Future Directions

The goals of retinal and visual prosthesis initiatives have evolved significantly over time. What began as an early 20th century exploration of the occipital cortex in seizure and projectile-wound patients led to the early development of visual prostheses like the Dobelle eye and the Artificial Silicon Retina, which provided the foundation for future work in restoring vision through visual prosthetics. As researchers develop advanced technology and a greater understanding of the visual system, prosthetic research will continue to advance, resulting in increased implant size and electrode density and improved device biocompatibility and surgical implantation protocols.

To date, more than 100 patients have been acutely or chronically implanted with retinal prostheses. In simulations and long-term studies, patients have experienced improvements in both visual acuity and quality of life. While

visual resolution is low, patients are able to do such things as locate bright objects on a dark table, discern grating patterns and identify simple objects including fruit, utensils and geometric shapes.[25] Implanted patients were also able to navigate a room and scored higher on the Functional Low-Vision Observer Rated Assessment, a quality-of-life assessment developed by the FDA for retinal prostheses.[37]

Despite these advances, visual prosthetics face several engineering obstacles. Ways to measure the success of a prosthesis include visual restoration and biocompatibility. Visual restoration refers to the ability of prostheses to improve a patient's visual acuity and visual field, while biocompatibility is reflected in the number of severe adverse events experienced by patients.

Visual acuity can be influenced by several factors, including electrode number and density, electrode overlap, understanding of intrinsic retinal processing and psychophysical performance. While the Alpha-IMS implant has demonstrated the highest visual acuity to-date (20/546), most prostheses are only able to obtain a visual acuity of 20/1000 or worse. It's believed that upwards of 600 to 1,000 pixels are required for restoration of useful vision; however, the majority of prostheses use 100 or fewer stimulating electrodes.[11] It's also difficult to reduce electrode size without raising charge densities to unsafe levels.[38] More research is also needed on visual processing in the retina and psychophysical performance associated with retinal stimulation.

In contrast, visual field restoration is often correlated with array size. It's currently believed that 300 µm of the retina roughly corresponds to 1 degree of the visual field.[18] The Argus II has developed the largest array (approximately 20 degrees, 3-mm diameter), but there are several surgical and physiological limitations to increasing array size.[14]

Biocompatibility is crucial for safety. While most prostheses have demonstrated a relatively low frequency of SAEs in humans, few studies have been conducted on the effects of chronic implantation.[1,18,39] However, some engineering characteristics that may play roles in biocompatibility include implant material, charge density, invasiveness and disease-induced change. While studies have been conducted on optimal materials for stimulation and implantation,[40] further long-term implantation studies in the retina are needed. Disease-induced changes in retinal physiology, separation of electrode-tissue interfaces and material considerations may also cause high charge densities, damage and/or gliosis.

Visual prosthesis research has made significant progress in improving the daily lives of patients suffering from diseases like RP and AMD. While several engineering limitations and challenges facing the field of retinal and visual prosthetics remain, recent advances in technology and physiology may soon lead to the use of prosthetics as a viable treatment for photodegenerative diseases. REVIEW

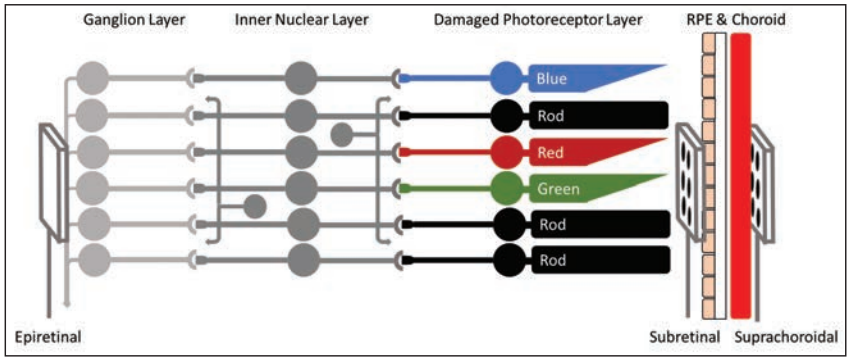

Figure 2. A brief overview of retinal stimulation targets: Photoreceptors in the retina transform light information into electrical and chemical signals. These signals are passed through the inner nuclear layer (bipolar cells, horizontal cells and amacrine cells) to reach the ganglion cell layer, which fires action potentials down the optic nerve. Stimulating arrays are typically implanted in the epiretinal space (between the vitreous and RGCs), in the subretinal space (between the damaged photoreceptors and retinal pigment epithelium) or in the suprachoroidal space (outside the choroid and beneath the sclera).

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The authors declare no financial interest in any product discussed.

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(Continued from page 41)

the wounds very well and keep the IOP at the high-normal range to encourage outflow of aqueous through the collector channels and out of the eye."

Dr. Kahook also shared his experience with the Dual Blade's intraoperative and postop complications. "The most common observation at the time of KDB treatment is reflux of blood from the collector channels that have been exposed by removal of the diseased trabecular meshwork," he says. "This is a good prognostic indicator that the treatment will result in measurable reduction of IOP postop. It is rare to have retained blood postop day one, and, in my experience, patients have very quick visual recovery on par with standalone cataract surgery." In a study that evaluated the effects of the Kahook Dual Blade on trabecular meshwork, across 157.5 ±26.3 degrees the procedure resulted in a decrease of IOP from 18.3 ±1.7 mmHg to 11.3 ±1.0 mmHg ($p<0.01$)[3].

Ab Interno Canaloplasty

Another new MIGS procedure is *ab interno* canaloplasty, which targets a population similar to the other MIGS devices. It's best utilized for those patients with mild to moderate glaucoma with elevated IOP.

Dr. Panarelli offers his insights into this procedure. "ABiC is considered to be a MIGS procedure as it can be performed through a microincisional approach (1.8-mm clear-corneal wound), is minimally traumatic to the targeted tissue and has reasonable efficacy and a favorable safety profile," he says. "When performing the procedure, the surgeon uses an illuminated microcatheter to first thread Schlemm's canal 360 degrees and then viscodilate that space as the catheter is withdrawn."

In a case series review of 122 eyes with a baseline IOP of 18.6 ±6.4 mmHg, mean IOP was reduced by 28.49 percent at six months (n=32). At six months, over half of the study population (n=17) were medication-free, with a mean IOP of 12.1 ±2.1 mmHg.[4]

"ABiC is an appealing new procedure, as it is conjunctiva-sparing, and one should encounter less bleeding when compared to similar procedures such as gonioscopy-assisted transluminal trabeculotomy and other angle-based procedures," Dr. Panarelli continues. "The biggest downside is the considerable learning curve that the surgeon faces, in terms of performing intraoperative gonioscopy as well as operating in the angle to locate Schlemm's canal. Like so many other new procedures, future prospective, randomized trials comparing ABiC to more traditional procedures will be needed to determine its true efficacy and its role in the glaucoma surgeon's armamentarium." REVIEW

Dr. Noecker is a consultant and clinical investigator to Glaukos. Dr. Ianchulev is a consultant for Alcon. Dr. Panarelli is a consultant to Allergan, Aerie and has received an honorarium from Glaukos. Dr. Francis is a Neomedix surgical trainer. Dr. Kahook is a consultant for Alcon and Allergan. He receives patent royalties from ClarVista Medical, New World Medical, J&J Vision and ShapeTech.

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Surgery 101: Managing Endothelial Risk

A stepwise approach to avoiding damage to the endothelium during cataract surgery.

Juan G. Gaviria, MD, Luis Escaf, MD, Juanita Londoño, MD, and Luz M. Melo, MD, Barranquilla, Colombia

As cataract surgeons, we are used to seeing happy patients on the first postoperative day with nicely centered IOLs in the bag, clear corneas and quiet eyes. However, achieving this level of satisfaction can be a challenge in patients at increased risk for pseudophakic bullous keratopathy, a feared complication of surgery, especially in countries with a high incidence of dense cataracts and poor access to corneal eye-bank tissue.[1]

In this article, we aim to provide a simple, five-step approach to increasing your success rate, which we define as clear corneas on postop day one for most of our patients.

The Challenge of PBK

The main cause of PBK is complicated cataract surgery with inadequate management of posterior capsular rupture or intraocular lenses placed in the anterior chamber. PBK can occur in 1 to 2 percent of patients after conventional cataract surgery, although this incidence can increase to 11 percent[2] and up to 24 percent[3] in cases with an endothelial cell count below 1,000 cells/mm^2. In about 5 percent of patients in need of cataract surgery, the surgeon will be able to identify one or more risk factors for PBK, including Fuchs' endothelial dystrophy, a shallow anterior chamber, angle closure glaucoma, previous eye surgery and/or very dense cataracts. Following is the systematic approach we take.

1. Recognize Eyes at Risk

Every eye undergoing cataract surgery is different, so the first step for success is to recognize eyes that are at risk for PBK. The following factors should be considered when assessing the risk of endothelial failure:

- ***Advanced age.*** Endothelial cell loss is known to occur physiologically over time.
- ***Systemic conditions.*** Conditions such as diabetes mellitus,[4] renal insufficiency[5] and chronic occlusive pulmonary disease[6] are known to decrease endothelial cell count and function.
- ***Medications.*** Drugs such as amantadine for Parkinson's disease or topical carbonic anhydrase inhibitors such as dorzolamide can affect corneal endothelial function. Also, medications such as tamsulosin increase the risk of posterior capsular rupture.
- ***Classification of nuclear cataract.*** Dense nuclear cataracts require more ultrasound energy and prolonged surgical time, are more prone to turbulence and chatter during phacoemulsification, and are technically more difficult to operate on.[7]
- ***Fuchs' endothelial dystrophy severity and other features.*** FED severity can be classified using the Krachmer scale: Mild FED includes patients with nonconfluent guttata; moderate FED has confluent guttata in a diameter between 1 and 5 mm; and severe FED has confluent guttata in an area larger than 5 mm, with or without corneal edema.

Moderate and severe FED cases have significantly decreased endothelial cell counts and, in some instances, increased corneal thickness.[8] Endothelial cell counts in patients with FED are often not reliable per se; and the surgeon must check the amount of guttata in the image to determine the quality of the endothelium, taking into consideration the coefficient of variability, hexagonality (polymorphism and polymegathism)[9] and the ultrasound pachymetry. Tradition-

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Table 1. Cataract Surgery Endothelial Risk Matrix

Endothelial Risk Score	0 (normal)	1 point	2 points	3 points	6 points
Fuchs classification (Krachmer)	0	1-2	3-4	5	6
Cell count	>2,000	<2,000	<1,500	<1,000	<500
CV and Hexagonality	<33 and >50%	<40 or >45%	>40 or <39%	>50 or <30%	>60 or <20%
U/S pachymetry	<540	540-575	576-624	625-649	>650
Anterior chamber	More than 4 mm	More than 3.5 mm	Less than 3.5 mm	Less than 2.7 mm	Less than 2 mm
LOCS III	NO 1 or 2	NO 3	NO 4	NO 5	NO 6

To obtain a risk score using this matrix, simply sum the points of a particular eye. For example: A 62-year old female patient presents with a LOCS III grade 5 nuclear cataract (3 points) in the right eye. She has FED grade 5 (3 points), an endothelial cell count of 508 cells/mm^2 (3 points) with a coefficient of variability of 39 and hexagonality of 37 percent (2 points), U/S pachymetry of 498 µm (0 points), and anterior chamber depth of 3.6 mm (0 points). Her total endothelial risk score for cataract surgery is: 3+3+3+2+0+0=11 (Low risk is 0-5, moderate is 6-10, high is 11-19 and very high risk is a score of 20 or more).

ally, a pachymetry greater than 600 µm indicated the need for a triple procedure (combined phacoemulsification, IOL implantation and endothelial transplantation), but this is shifting towards a pachymetry of 630 to 640 µm based on more recent research.[10] A newer method, the measurement of epithelial corneal backscatter, seems promising, but it's still not clinically available to most cataract surgeons.[11]

With current diagnostic methods, we lack a specific number in terms of endothelial cell count or pachymetry to determine if a FED-affected cornea will be able to withstand cataract surgery and remain transparent or if it will require a triple procedure.[12] Patients with advanced FED manifest clinically with blurred vision in the morning, which then improves as the day progresses. These symptoms indicate endothelial dysfunction and are extremely important to elicit during your preoperative evaluation.

• ***Previous eye surgery.*** Previous ocular surgery such as penetrating keratoplasty, peripheral iridotomy, trabeculectomy, intraocular lens implantation, glaucoma valve implantation or previous retinal surgery with the use of silicone oil can decrease the endothelial cell count and should be considered risk factors for PBK.

• ***Small eyes.*** Eyes with a very shallow anterior chamber, short axial length and primary angle closure glaucoma tend to have lower endothelial cell counts. Intraoperatively, the distance between the cornea and the phacoemulsification tip is naturally reduced in these eyes, which implies a higher amount of ultrasound energy indirectly delivered to the endothelium.

2. Score the Risk

The second step for success is to score the level of risk for the eye. In order to evaluate the risk, we evaluate:

• the quality of the endothelium on the Krachmer scale for FED, endothelial cell count and ultrasound pachymetry;

• anterior chamber depth by conventional biometry or other methods; and

• the degree of cataract. We use the LOCS III classification, but another method can be substituted according to your preference.

Variables evaluated in the risk matrix *(appearing in Table 1)* are the severity of FED, endothelial cell count, coefficient of variability, hexagonality, ultrasound pachymetry, anterior chamber depth and LOCS III cataract grade classification. Interpretation of the risk score follows in step 3.

3. Customize the Surgery

The third step for success is to be aware of your surgical options and use them according to the score calculated in step 2:

• ***Low risk (0 to 5).*** In low-risk patients, such as those with soft cataracts, normal ACD and few guttata with no other corneal abnormalities, a normal phacoemulsification procedure with controlled fluidics can be performed with very low risk.

• ***Moderate risk (6 to 10).*** An example of a moderate-risk case would be someone with moderate FED, with a cell count above 1,500 cells/mm^2 and a cataract LOCS III grade 4. In such a patient, prechopping, ultrasound-sparing techniques (femtosecond laser-assisted, Akahoshi prechop, ultrachop,[13] etc.) should be used. Also, dispersive OVD injection should be repeated every three to five units of effective phacoemulsification time during quadrant removal.

• ***High risk (Score 11 to 19).*** Zero-ultrasound techniques such as extra-

capsular cataract extraction or manual small incision cataract surgery should be considered in these cases, paying special attention to avoiding contact between the nucleus and the endothelium, as endothelial contact can be just as damaging to the compromised endothelium as a normal phaco.

Viscodynamic extraction is another zero-phaco technique that can be used. It involves a sclero-corneal tunnel, small fragmentation of the nucleus using any method (femtosecond laser,[14] ultrachopper[15] or Akahoshi prechopper), and subsequent fragment removal through the sclerocorneal wound while dispersive viscoelastic is injected liberally into the anterior chamber to push the fragments out of the eye.

• ***Very high risk (20+).*** In these patients, the surgeon should consider a triple procedure with Descemet's stripping endothelial keratoplasty, ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty, according to his/her preference.

4. Avoid Intraoperative Damage

Adhere to the three pillars of endothelial protection: Use minimum or zero ultrasound energy near the corneal endothelium; maintain a stable, closed fluidics system; and keep a normal-to-low IOP.

Increasing the distance from the cornea to the tip of the phaco probe reduces the amount of effective U/S energy at the level of the endothelium. Working on the iris plane, as far as possible from the cornea, reduces the likelihood of corneal damage. Holding the U/S tip downwards, away from the endothelium, can also avoid the direct effects of U/S energy.[16] Similarly, placing dispersive viscoelastic for every three to five units of cumulative dissipated energy against the endothelium creates a barrier between the U/S tip and the cornea.[17,18]

Working in a closed system (i.e., avoiding fluid loss through the paracentesis) prevents fragments from contacting the endothelium and allows for a deeper AC. Slow-motion parameters reduce turbulence and chatter, help reduce the risk of fragments hitting the endothelium[19] and help avoid posterior capsular rupture, which is a major risk factor for PBK.

We routinely favor the use of preop IV mannitol or oral acetazolamide if the anterior chamber is less than 2.8 mm deep or there is history of glaucoma. Higher IOPs can induce more corneal endothelial damage and low IOPs can result in anterior chamber shallowing with undesired consequences.

5. Discuss the Risks

Have a conversation with the patient about the risks and possible complications of the case. Patients have the right to understand their problem as well as their alternatives. Regional differences and the availability of corneal tissue play a significant role in the surgeon's decision. Similarly, each surgeon should be aware of his own level of expertise both with cataract surgery and endothelial transplant techniques in order to decide the best option for the patient at any given time.

Performing early surgery can be best in soft cataracts, while waiting until the cataract has caused significant visual loss can be the best option in high-risk cases when corneal tissue isn't readily available. In advanced FED cases with moderate cataracts, it can be acceptable to perform an U/S-sparing cataract surgery technique to reduce the possibility of corneal decompensation, but the patient should be aware of the possibility of endothelial corneal transplantation in the near future.

We hope that this discussion of the major risk factors and our simple tool for risk stratification of corneal endothelial damage in the setting of cataract surgery, has been helpful. The selection of surgical technique will depend on the surgeon's preference and expertise, and the three pillars of endothelial protection provide a simple guide every time we decide to perform phaco. By following this approach, the surgeon will be more likely to obtain clear corneas on the first postoperative day for most cases, and we'll all help conserve a precious and limited resource: corneal tissue. REVIEW

The authors practice at Clinica Oftalmológica del Caribe in Barranquilla.

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Measuring IOP Fluctuations in NTG

Researchers from the Department of Ophthalmology at the University of Toyama, Japan, compared the fluctuation of intraocular pressure in normal-tension glaucoma patients and individuals without glaucoma. They obtained continuous IOP values using a Sensimed Triggerfish contact lens sensor.

The eyes of 12 nonglaucoma subjects and 14 NTG patients were examined. In all 26 subjects, IOP fluctuation was measured continuously for 24 hours with the Triggerfish. The range of IOP fluctuation was analyzed, and cutoff level of IOP fluctuation was calculated using receiver operating characteristic curve analyses.

The mean IOP in the NTG eyes was 11.5 ±2.4 mmHg, and in the nonglaucoma eyes it was 12.7 ±2.0 mmHg, a statistically insignificant difference (p=0.175). The 24-hour range of IOP fluctuations in the NTG group was significantly larger than that of the nonglaucoma group, however (p=0.007). The percentage of NTG patients who had the peak time of IOP fluctuation during nocturnal sleep was 57.1 percent, whereas the corresponding rate for the nonglaucoma eyes was 91.7 percent.

The range of IOP fluctuations was larger in the eyes with NTG than in the nonglaucoma eyes. This larger fluctuation might be one of the factors underlying the aggravation of the visual field by NTG. Measurements of 24-hour continuous IOP might be a useful way to distinguish NTG from nonglaucoma eyes, researchers say.

J Glaucoma 2017;26:195-200
Tojo N, Abe S, Ishida M, Yagou T, Hayashi A.

Tomography Systems in Corneas with Keratoconus

In this reliability analysis of the Orbscan II, Pentacam HR and Galilei tomography systems, researchers from Auckland, New Zealand, studied the repeatability and agreement of keratometry and pachymetry measurements obtained using these three tomographers in eyes with keratoconus. The researchers looked at 50 eyes of 50 patients with keratoconus. The observational procedure focused on: steep keratometry; flat keratometry; central corneal thickness; and thinnest corneal thickness.

Repeatability was assessed using within-subject standard deviation, coefficient of variation and intraclass correlation coefficient. Bland-Altman plots and 95 percent limits of agreement (mean difference ±1.96 multiplied by standard deviation) were used to evaluate agreement between device pairs.

For all studied parameters, ICC was >0.97, with the least repeatable measurements obtained using Orbscan II. Mean steep keratometry values were similar while mean flat keratometry values were significantly different among all devices. The Galilei and Pentacam HR had the lowest 95 percent LoA for both CCT and TCT. There were no significant differences in mean CCT between Galilei and Pentacam HR. Mean Orbscan II CCT measurements weren't significantly different overall but had wide 95 percent LoA with Pentacam HR (-47.95 to 58.09 µm) and Galilei (-43.70 to 53.91 µm). Mean Orbscan II CCT measurements were significantly lower when an acoustic factor of 0.92 was applied (-33.6 µm vs Pentacam HR, p<0.001; -33.6 µm vs Galilei; p<0.001).

The researchers say that keratometric and pachymetric measurements of keratoconic eyes obtained by Galilei, Orbscan II and Pentacam were disparate. Although overall repeatability was high for all instruments, measurements were less repeatable with Orbscan II in comparison to Pentacam HR and Galilei.

Am J Ophthalmol 2017;175:122-128
Meyer J, Gokul A, Vellara H, Prime Z, McGhee C.

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WET LAB PROGRAMS

Dear Ophthalmology Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 3rd-Year Ophthalmology Resident Wet Lab Programs for 2017 in Fort Worth, Texas. The programs offer a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Best regards,
Kendall Donaldson, MD, Weldon Haw, MD & Mitch Weikert, MD
(Program Directors)

Third-Year Resident Wet Lab Programs 2017:

August 18-19
Fort Worth, TX
Course Director:
Weldon Haw, MD

August 25-26
Fort Worth, TX
Course Director:
Mitch Weikert, MD

September 8-9
Fort Worth, TX
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Course Director:
Kendall Donaldson, MD

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Email: dholmes@postgradhealthed.com • Call: Denette Holmes 866-627-0714

Courses are restricted to 3rd-year residents enrolled in an ophthalmology resident program and within their third year at the time of the course. There is no registration fee for these activities. Air, ground transportation in Forth Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

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 Amedco and Postgraduate Healthcare Education. Amedco is accredited by the ACCME to provide continuing medical education for physicians.

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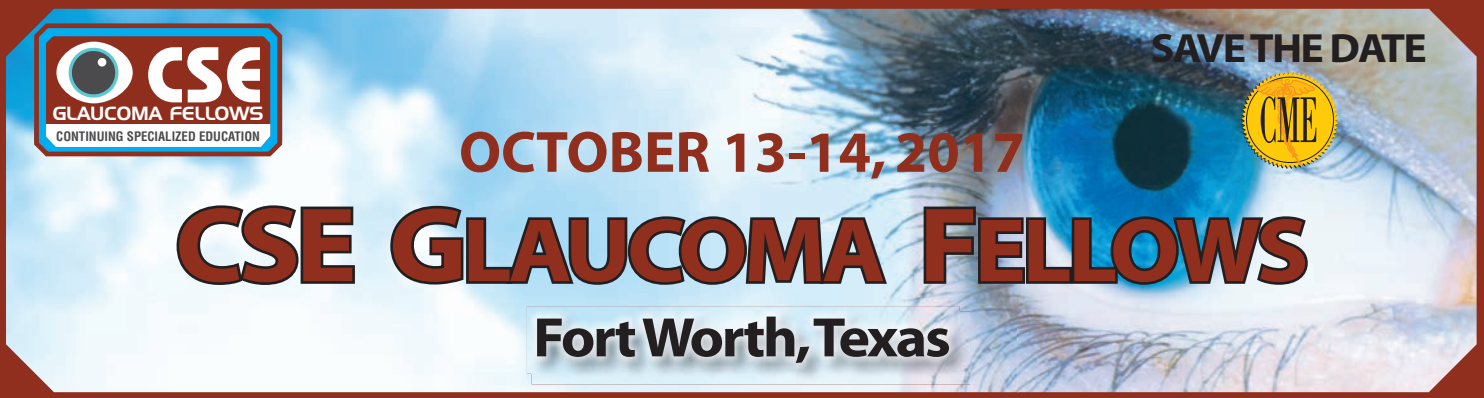

Dear Fellowship Program Director and Coordinator,

We would like to invite you to review the upcoming 2017 Glaucoma Fellowship Program and Wet Lab in Fort Worth at the Renaissance Worthington hotel. The program offers a unique educational opportunity for fellows by providing the chance to meet and exchange ideas with some of the most respected thought leaders in glaucoma. The Glaucoma Fellows Program and Wet Lab is designed to provide your fellows with a state-of-the-art didactic and wet lab experience. The program also serves as an opportunity for your fellows to network with fellows from other programs.

After reviewing the material, it is our hope that you will select and encourage your fellows to attend this educational activity which is CME accredited to ensure fair balance.

Sincerely,
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Stanford, CA

Wet Lab Directors:

Douglas J. Rhee, MD
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Ronald Fellman, MD
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Participants in this course must be enrolled in a glaucoma fellowship program at the time of the course.
There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

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Reichert's ClearChart Digital Acuity Systems

Reichert Technologies, Buffalo, N.Y., has announced three new ClearChart Digital Acuity Systems: ClearChart 4 Digital Acuity System; ClearChart 4X Enhanced Digital Acuity System; and ClearChart 4P Polarized Digital Acuity System.

These new systems all feature 24-inch, high-resolution, lightweight LED displays. Reichert says they come equipped with an easy-to-navigate interface controlled from the Phoroptor VRx Digital Refraction System, SightChek Digital Phoroptor or a simple infrared remote. The systems also require no separate components or software.

The ClearChart 4X and ClearChart 4P allow users to import images and videos from a USB drive. They also include ETDRS, contrast sensitivity and patient education slides. All models can be configured for standard or mirrored viewing for refracting distances from 6 to 24.6 feet.

For more information on Reichert's ClearChart systems, visit reichert.com/clearchart.

Bausch + Lomb Introduces Vitesse

In late April, Bausch + Lomb announced that Vitesse, a hypersonic, completely open-port vitrectomy system, received FDA clearance. This news follows close behind the company's FDA approval for its Stellaris Elite Vision Enhancement System. Vitesse will be available exclusively on the Stellaris Elite in the coming year.

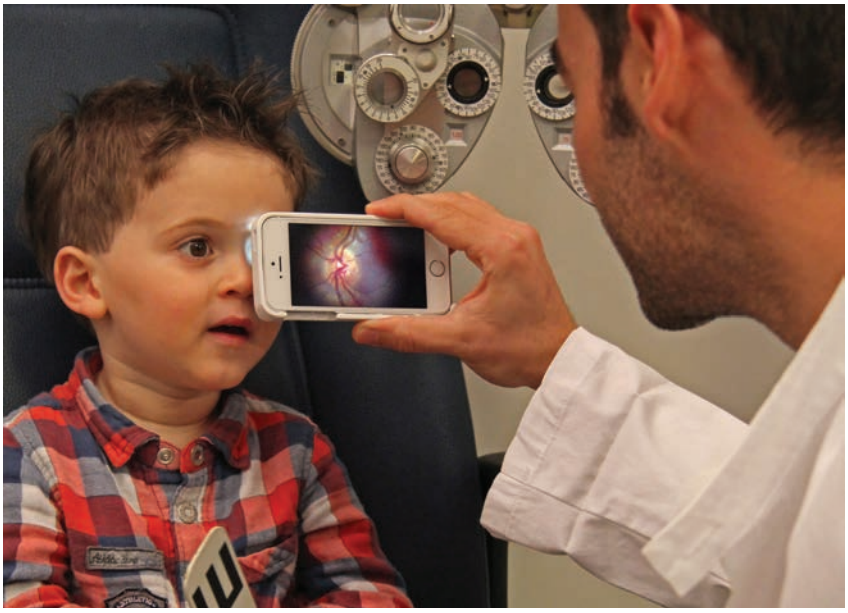
Vitesse's design consists of a single lumen with a fixed, open port for consistent flow. Bausch + Lomb says that this design creates a highly localized tissue liquefication zone, which liquefies the vitreous at the edge of the port before aspiration. The company hopes that this new technology will eliminate the traditional "guillotine-style" vitrectomy cutter, which was introduced 40 years ago.

For more information on Bausch + Lomb's Vitesse and Stellaris Elite, visit bausch.com/our-products.

D-EYE Upgrades System

In late April, D-EYE released an upgrade to its smartphone-based retinal imaging system. This application upgrade, called ImageSelect, allows users to convert high-definition video fundoscopy into images that can be edited and saved as PDFs, which can then be shared and transferred to other devices.

D-EYE also recently introduced a LAN share feature that allows images and videos to be moved across a local area network to Window's PCs and Macs.



D-EYE

This article has no commercial sponsorship.

For more information on ImageSelect, visit d-eyecare.com.

Haag-Streit Fundus Module 300

Haag-Streit recently announced it received FDA approval for its Fundus Module 300 slit lamp attachment. It attaches directly to the slit lamp for integration into the examination process, unlike handheld fundus camera devices, the company says.

The camera is controlled with Haag-Streit's control panel (RM02), and images captured by the device are transferred to Haag-Streit's EyeSuite software, allowing for more convenient and efficient examinations for both physicians and their patients, Haag-Streit says. It is compatible with the BQ 900, BP 900, BI 900 and BM 900 slit lamps. It can also be used in combination with the IM 900 or IM 600.

For more information on Haag-Streit's Fundus Module 300, visit hsdriven.com/fundus.

Oasis Debuts Punctal Plug

Oasis recently added a new punctal plug to its Soft Plug punctal occlusion line: the Soft Plug Extended Duration 180. It's made of an absorbable polydioxanone material and can last up to 180 days. The new plugs come in three sizes: 0.3 x 2.0 mm; 0.4 x 2.0 mm; and 0.5 x 2.0 mm.

In addition to the plugs, Oasis recently added its Lid & Lash pre-soaked pads, available with or without Tea Tree Oil, to its line of daily lid-hygiene solutions. Both versions of the pads come with 60 pads, for a one-month supply. Oasis claims that a third-party study found that the skin around the eye was 20 percent more hydrated within two weeks of daily use of Lid & Lash.

For more information on OASIS Medical's Punctal Plug and Eyelid pads, visit oasismedical.com.

Allergan TrueTear

Allergan announced that the FDA recently approved its TrueTear Intranasal Tear Neurostimulator, the first and only FDA-cleared device that temporarily increases tear production in a neurostimulation.

The handheld stimulator uses daily disposable tips that are inserted into the nasal cavity to induce tear production through neurostimulation. Allergan says two clinical studies showed positive safety and efficacy of the device in 145 aqueous-deficient dry-eye patients.

For more information on the TrueTear or the two clinical studies, visit allergan.com.

Optovue's High-Density OCT Angiography

By releasing AngioVueHD Imaging, Optovue says it has become the first company to offer higher density OCTA imaging that improves resolution and peripheral visualization of vasculature in the eye. Optovue claims that higher resolution and increase in sampling points will enable physicians to more closely study the fine vasculature in the eye for changes that could indicate ocular disease.

According to the company, the standard field-of-view for the best image quality measures 3 x 3 mm, while the AngioVueHD update allows equivalent image quality in the 6 x 6 mm field-of-view.

Optovue has also recently released the AngioVueHD Montage, which combines two high-density images (one at the central macular region and the other at the optic disc), resulting in a 10 x 6 mm field of view. The company says this is useful for imaging vasculature in potential pathologies that may extend into the periphery of the imaging plane.

For more information on the AngioVueHD and AngioVueHD Montage, visit optovue.com.

Lucentis Approved for DR

Genentech's Lucentis ranibizumab injection 0.3 mg is now approved for the monthly treatment of all forms of diabetic retinopathy, making it the only drug with this distinction.

The injection received FDA approval based on an analysis of the NIH-funded Diabetic Retinopathy Clinical Research Network's Protocol S study, in which Lucentis was compared to panretinal laser treatment in diabetic retinopathy patients with and without diabetic macular edema. Patients both with and without DME in the Lucentis group experienced improvements in the severity of their retinopathy.

For more information on Lucentis, visit gene.com/patients/medicines/lucentis.

REVIEW Medicare Q&A

(Continued from page 21)

allowable for the technical component of the lesser-valued test when more than one test is performed on the same day.

Q If Medicare or other payer does not cover external ocular photography, may we charge the patient?

A Sometimes. Explain to the patient why the test is necessary, and that Medicare or other third party payer will likely deny the claim. Ask the patient to assume financial responsibility for the charge. A financial waiver can take several forms.

An Advance Beneficiary Notice of Noncoverage is required for services where Part B Medicare coverage is ambiguous or doubtful, and may be useful where a service is never covered.

For non-Medicare beneficiaries, a Notice of Exclusion from Health Plan Benefits is an alternative to an ABN.

For Part C Medicare, determination of benefits is required to identify beneficiary financial responsibility prior to performing either noncovered or potentially noncovered services; MA Plans may each have their own process and waiver forms. Be sure to check.

Q Is external ocular photography bundled with other services?

A Yes. According to Medicare's National Correct Coding Initiative, 92285 is bundled with the surgical codes for blepharoplasty procedures (15820-15824). Also, gonioscopy (92020) and the technician exam (99211) are bundled with external ocular photography. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

REVIEW Advertising Index

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Practice For Sale

A 60-year-old man presents with worsening floaters and a slow decrease in visual acuity.

Jordan D. Deaner, MD, and Carol L. Shields, MD

Presentation

A 60-year-old Caucasian man presented with a chief complaint of progressively worsening floaters in both eyes, with the left eye being worse than the right. His symptoms began three months prior to presentation, and the floaters progressively increased over the three weeks preceding his presentation. He also noted a gradual decrease in vision OS.

Medical History

The patient had no prior ocular or medical history. His past surgical history was significant only for inguinal hernia surgery. He smoked a pack per day for approximately 20 years. Family history was non-contributory and there were no known drug allergies. He was not taking any medications. Review of systems revealed no new findings.

Examination

On examination his best corrected visual acuity was 20/40 OD and 20/200 OS. His pupils were equal, round, reactive to light with no relative afferent pupillary defect. Extraocular eye movements were full bilaterally. His intraocular pressures were 20 mmHg OD and 19 mmHg OS with applanation tonometry. Slit lamp examination was only remarkable for 1-2+ fine vitreous cells bilaterally.

Funduscopically, the right eye was normal with the exception of mild vitreous haze. The left eye revealed multiple creamy yellow subretinal pigment epithelial lesions in the temporal macula, suspicious for a subretinal, sub-RPE or choroidal infiltrative process *(See Figure 1)*.

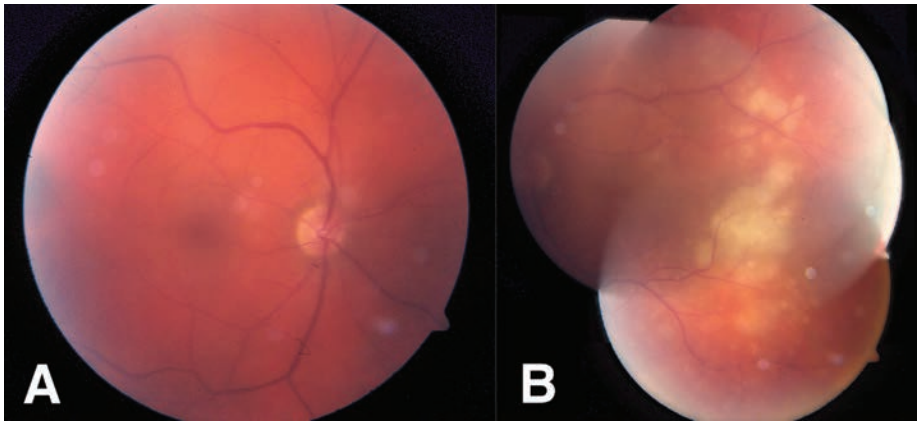

Figure 1. Fundus photograph of the right eye demonstrating slight vitreous haze but otherwise normal fundus (A) and the left eye demonstrating multiple creamy yellow sub-RPE lesions in the temporal macula (B).

What is your differential diagnosis? What further workup would you pursue? Please turn to page 72.

Differential Diagnosis

The differential diagnosis of retinal or choroidal infiltrative lesions is broad and includes infectious, inflammatory and neoplastic conditions. The most important are listed below:

- Infectious
  - acute retinal necrosis
  - fungal endophthalmitis
  - bacterial endophthalmitis
  - syphilis
  - toxoplasmosis retinochoroiditis
  - tuberculosis
- Inflammatory
  - sarcoidosis
  - acute posterior multifocal placoid pigment
- Epitheliopathy
  - multifocal choroiditis
  - serpiginous choroidopathy
  - idiopathic posterior uveitis
  - autoimmune choroidopathy
  - CTLA4 choroidopathy
- Neoplastic
  - vitreoretinal lymphoma
  - uveal lymphoma
  - uveal metastasis

Diagnosis and Workup

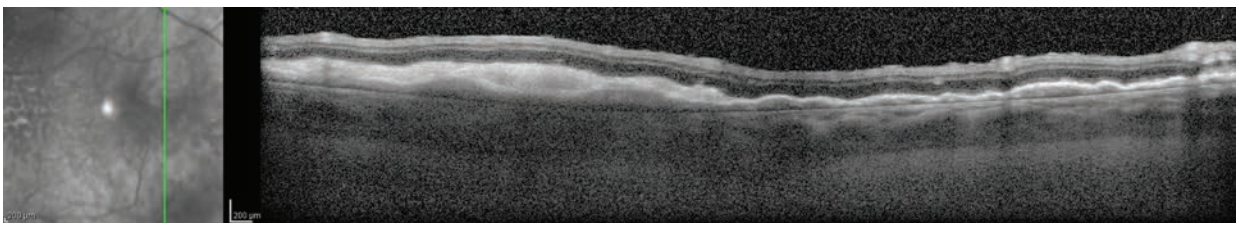

Figure 2. OCT of the temporal macula demonstrating an undulating configuration of hyper-reflective sub-RPE deposits below an intact retina.

Given the patient's age and presentation, vitreoretinal lymphoma was at the top of the differential diagnosis. Diagnostic testing using optical coherence topography revealed undulating, hyper-reflective sub-RPE deposits below an intact retina *(See Figure 2).* Fundus autofluorescence demonstrated mottled hyperautofluorescent RPE in the macular region at the site of the sub-RPE lesions. *(See Figure 3)* Magnetic resonance imaging of the brain and orbits revealed thickening and layering of material in the posterior aspect of the left eye, but otherwise normal orbits. A lumbar puncture was performed and cerebrospinal fluid studies were within normal limits. Cytology did not demonstrate abnormal lymphocytes.

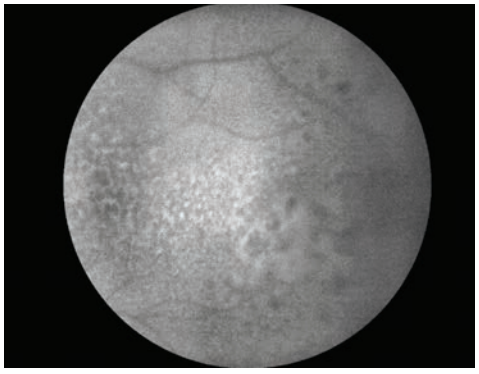

Figure 3. Fundus autofluorescence of the temporal macula demonstrating mottled hyperautofluorescence in the region of the lesion.

The patient subsequently underwent fine needle aspiration biopsy of the sub-RPE deposits. Cytopathological examination revealed a few small, well-differentiated lymphocytes not typical of lymphoma, but consistent with a diagnosis of chronic vitreous inflammation. Knowing that multiple biopsies are often required to demonstrate positive pathology for ocular lymphoma,[1] a vitreous biopsy was obtained via pars plana vitrectomy. Microscopic examination of the second biopsy revealed small, well-differentiated lymphocytes mixed with larger dendritic histiocytes consistent with a diagnosis of chronic vitreous inflammation.

After two negative biopsies for lymphoma, it was decided to treat the patient for presumed autoimmune uveitis. The patient received 40 mg of sub-Tenon's fascia Kenalog. Nine days after the administration of STK, repeat fundoscopic examination revealed rapid enlargement and coalescence of the creamy yellow sub-RPE lesions, in addition to intraretinal hemorrhage along the superior arcade *(See Figure 4).* Concern for persistent tumor, rather than inflammation, was raised, despite the negative biopsies.

Rapid expansion of the lesions following injection of STK was also concerning for possible infectious etiolo-

gies and the differential diagnosis was refocused to include HIV ELISA, ANCA, CBC, CMP, ESR, RPR, FTA-ABS, quantiferon gold, toxoplasmosis and bartonella titers. An anterior chamber tap was performed and aqueous was sent for PCR testing to assess for toxoplasmosis, CMV, VZV and HSV. The patient subsequently underwent a second PPV, diagnostic retinectomy and drainage of the subretinal fluid. The SRF was sent for fungal and bacterial stain, culture and PCR analysis.

The previous serological workup and PCR results didn't identify a specific etiology. Fungal, Gram stain and AFB stain were negative for microorganisms. Fungal and bacterial cultures showed no growth. Pathological examination of the retinal biopsy demonstrated a segment of extensively necrotic retina diffusely infiltrated with small lymphocytes *(See Figure 5)*. Immunohistochemistry showed diffuse positive reactivity for B-cell marker CD20 *(See Figure 5)*, consistent with a diagnosis of B-cell lymphoma. The patient was diagnosed with bilateral primary vitreoretinal lymphoma without central nervous system involvement.

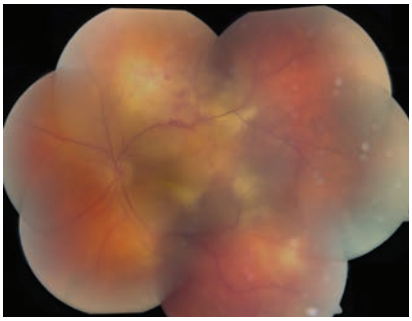

Figure 4. The left eye demonstrated rapid enlargement and coalescence of creamy yellow sub-RPE lesions, in addition to intraretinal hemorrhage along the superior arcade after administration of STK.

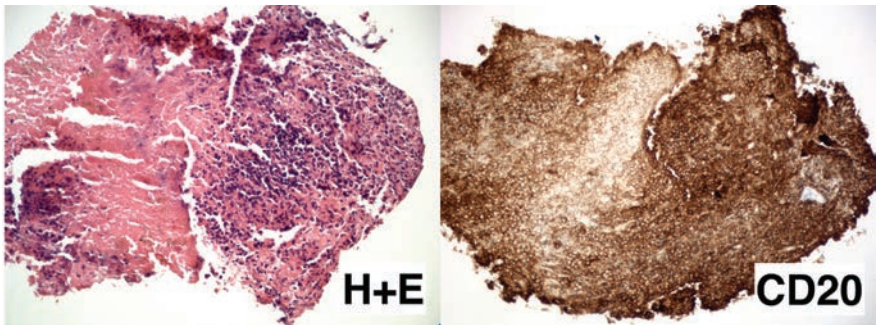

Figure 5. Hemotoxalin and eosin preparation (low power, left) of the retinal biopsy demonstrating extensively necrotic retina diffusely infiltrated by small lymphocytes with uniform positive reactivity to the B-cell marker CD20 (right).

Treatment

The patient was treated with bilateral intravitreal methotrexate injections. After the twelfth injection OD and the sixth OS he had resolution of the floaters and vitreous cells OU, and involution of the sub-RPE lesions OS. His vision after the final treatment was 20/20 OD and hand motion OS.

Discussion

Primary vitreoretinal lymphoma is a subtype of intraocular lymphoma that includes primary CNS lymphoma with vitreoretinal involvement, termed primary vitreoretinal lymphoma. PVRL is a variant of PCNSL that originates in the eye and demonstrates extension to the CNS.[2] Most patients with PVRL present symptomatically, most commonly with blurred vision (71 to 86 percent) or floaters (25 to 43 percent).[3,4] However, up to 17 percent are completely asymptomatic at the time of presentation.[4] Clinically, 64 to 80 percent of patients have bilateral involvement at the time of presentation.[3,4]

By examination, slit lamp biomicroscopy classically reveals vitreous cells in 86 to 88 percent of patients.[3,4] These cells are unique in that they are relatively homogenous, appear larger than ordinary inflammatory cells, don't clump into reactive clusters and cause an "aurora borealis" appearance as the cells line up along the vitreous fibrils.[5] Fundus examination characteristically shows greasy, yellow, sub-RPE infiltrates that can enlarge and coalesce over a short period of time.[5] Other less-common features include perivasculitis and exudative retinal detachment.[5]

Ancillary testing of PVRL is important to guide the diagnostic evaluation, but pathology is required to make a definitive diagnosis. OCT imaging demonstrates a multifocal, dome-shaped elevation of the RPE from sub-RPE tumor deposits, retinal elevation or thickening from direct tumor infiltration, and cystoid macular edema from the associated inflammatory reaction.[6] Fluorescein angiography often shows clusters of round hyper- or hypofluorescent lesions, in both the early and late phases, along with heterogenous choroidal fluorescence.[5] Fundus autofluorescence demonstrates multiple weak or strong hyperautofluorescent spots, suggesting overlapping of PVRL and RPE cells, and hypoautofluorescent areas that

suggest PVRL cells above the RPE, or RPE atrophy.[5]

Fine-needle aspiration biopsy or pars plana vitrectomy with cytopathologic diagnosis remains the mainstay of diagnosis of this condition. In questionable cases, Myd88 mutation testing can guide the diagnosis of PVRL and is positive in 83 percent of cases.[7] Measurement of IL-6 and IL-10 in aqueous or vitreous fluid can raise the suspicion for PVRL, but an elevated IL-10/IL-6 isn't diagnostic.[8]

Cytopathological features can be varied in PVRL. PVRL cells are large, atypical lymphoid cells with large, irregular nuclei, prominent nucleoli and scant basophilic cytoplasm. These cells are prone to spontaneous necrosis, which may contribute to the high false-negative rate of pathologic diagnosis, so careful and prompt processing is critical.[9] One study documented that multiple vitreous biopsies are often required to demonstrate adequate pathology in PVRL, requiring three vitreous biopsies in some cases.[1] MRI of the brain and LP should be performed in all individuals suspicious for PVRL to assess for CNS involvement.[5] The findings of CNS lesions on MRI or lymphoma cells in the CSF support the diagnosis of PVRL and can negate the need for ocular biopsy.[5]

There's no consensus defining the single best therapy for PVRL. Treatment options include intravitreal methotrexate or rituximab, and external beam radiation therapy (EBRT).[10-12] The largest reported series of patients treated with intravitreal methotrexate included 44 eyes in 26 patients using an induction-consolidation-maintenance regimen.[10] All cases achieved clinical remission after an average of 6.4 injections with 95 percent of eyes responding to 13 injections or less.[10] None of the patients treated with intravitreal methotrexate relapsed during a follow-up period ranging from 41 to 107 months.[10]

Both animal and human studies suggest that intravitreal rituximab may require fewer injections (median: four) and have fewer side effects than methotrexate, but the trials are small and follow-up is short, so further investigation is required.[11] EBRT can be particularly useful in treating PVRL in patients who have bilateral involvement, may not be able to tolerate intravitreal chemotherapy and/or can't return for multiple injections.[12] There's no obvious difference in outcomes compared to methotrexate, but no head-to-head trials have been performed to compare their efficacy.[12]

The treatment for PVRL with CNS spread is similar to that for PCNSL with or without vitreous involvement, with systemic intravenous methotrexate the most commonly used agent.[13] A large, multicenter, retrospective study found that the median progression-free and overall survival was 18 and 31 months, respectively.[13]

The prognosis of PVRL is unfortunately bleak, with 65 to 90 percent of patients going on to develop CNS lymphoma during their lifetime.[5] In a large multicenter study, of 60 patients diagnosed with PVRL with a negative MRI done at the time of diagnosis, 15 percent were found to have positive CSF cytology, indicating subclinical involvement of the CNS at the time of diagnosis.[2] The study's authors went on to note that of 83 patients initially diagnosed with and treated for localized PVRL, 56 percent relapsed and 62 percent went on to have CNS involvement by 19 months.[2] Median progression-free time and overall survival were 30 and 58 months, respectively, and were unaffected by treatment type.[2] Regardless of which therapy is used, there's a very high likelihood of local recurrence and CNS involvement, justifying the need for periodic CNS monitoring with MRI.

Although there is a high likelihood for PRVL to progress to CNS disease, a 17-center European study showed there was no significant difference in the development of CNS lymphoma between patients treated with local chemotherapy or radiotherapy versus prophylactic systemic therapy.[14] CNS involvement occurred in 32 to 43 percent (median time of occurrence: 49 months) and wasn't statistically different between the treatment groups.[14]

In summary, a 60-year-old man presented with bilateral floaters, vitritis and rapidly progressing retinal lesions of the left eye. Two biopsies demonstrated chronic inflammation. A third biopsy of the retina and vitreous revealed a diagnosis of primary vitreoretinal lymphoma. The patient was successfully treated with intravitreal methotrexate to remission. He'll be monitored for recurrence and involvement of the central nevous system. REVIEW

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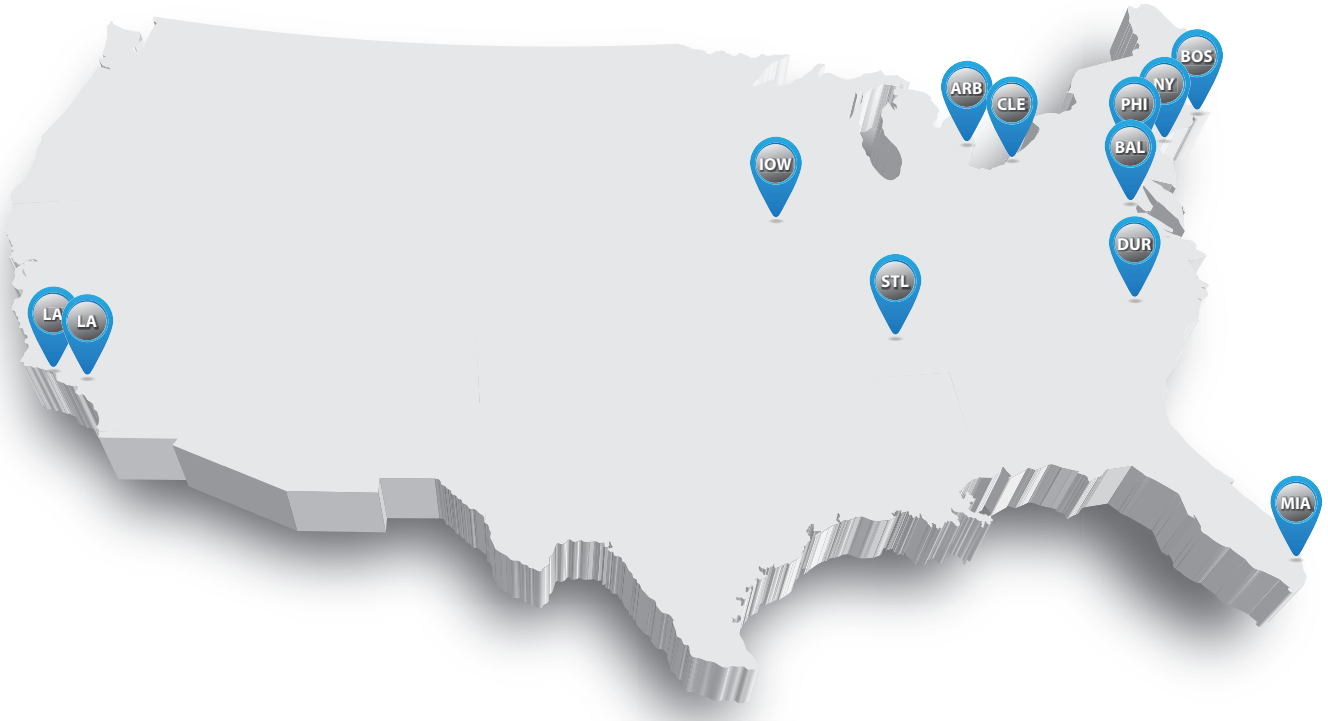

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