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REVIEW NEWS
Volume XX • No. 3 • March 2013

FDA Approval for Argus II Retinal Prosthesis System

After more than 20 years of research and development, Second Sight Medical Products announced that its Argus II Retinal Prosthesis System has received U.S. market approval from the Food and Drug Administration to treat individuals with late-stage retinitis pigmentosa. This announcement follows receipt of the European approval in 2011. *(For a more extensive description of Argus II, see p. 60.)*

"We are thrilled to be able to offer the only FDA-approved, long-term therapy for people suffering from advanced RP," said Robert Greenberg, MD, PhD, president and CEO of Second Sight. "With this approval, we look forward to building a strong surgical network in the United States and recruiting new hospitals that will offer the Argus II retinal implant. This is a game-changer in sight-affecting diseases, that represents a huge step forward for the field and for these patients who were without any available treatment options until now."

Argus II is intended to provide electrical stimulation of the retina to induce visual perception in blind individuals with retinitis pigmentosa and has the capacity to offer life-changing visual capabilities to those currently unable to see anything except, at best, extremely bright lights.

Although the resulting vision is not the same as when these patients had normal vision, investigators involved in the clinical trial of the Argus II are eager about the approval. "It is incredibly exciting to have FDA approval to begin implanting the Argus II and provide some restoration of vision to patients blinded from RP. In the patients that have been implanted to date, the improvement in the quality of life has been invaluable," said Mark Humayun, MD, PhD, Cornelius Pings Professor of Biomedical Engineering and Professor of Ophthalmology, Biomedical Engineering, Cell and Neurobiology, Keck School of Medicine of USC and USC Viterbi School of Engineering, University of Southern California.

"The fact that many patients can use the Argus implant in their activities of daily living such as recognizing large letters, locating the position of objects, and more, has been beyond our wildest dreams, yet the promise to the patients is real and we expect it only to improve over time."

With approval from the FDA, the Argus II is slated to be available later this year in clinical centers across the country. Second Sight will be actively adding sites to make the therapy more readily available and encourages interested facilities and patients to contact them.

The Argus II System works by converting video images captured by a miniature camera housed in the patient's glasses into a series of small electrical pulses that are transmitted wirelessly to an array of electrodes on the surface of the retina. These pulses are intended to stimulate the retina's remaining cells resulting in the corresponding perception of patterns of light in the brain. The patient then learns to interpret these visual patterns thereby regaining some visual function. Argus II is the only approved retinal prosthesis anywhere in the world. For more information, visit 2-sight.com.

CATT Analysis Sheds Light on AMD And Genetics

New findings from the Comparison of AMD Treatment Trials (CATT) show that although certain gene variants may predict whether a person is likely to develop age-related macular degeneration, these genes do not predict how patients will respond to Lucentis and Avastin, the two medications most widely used to treat wet AMD. This new data, published online in *Ophthalmology*, found no significant association between four gene variants and outcomes that measured the patients' responses to treatment.

The CATT genetics research team wanted to learn whether the major AMD risk genes could be useful in tailoring treatment with Avastin and Lucentis to individual patients' needs to boost treatment effectiveness and safety for patients. The main CATT study had confirmed that both medications significantly reduce or even reverse vision loss in many patients with wet AMD, but that study also found that treatment

effectiveness varied among patients. The CATT genetics study, led by Stephanie Hagstrom, PhD, at the Cole Eye Institute at the Cleveland Clinic, clearly showed that the major AMD risk alleles do not predict patients' response to treatment.

This genetics study cohort comprised 73 percent of the 1,149 CATT participants. Cohort patients were evaluated for four gene variants linked to AMD risk: CFH, ARMS2, HTRA1 and C3. The patients' genotypes were then compared to their responses to treatment with Lucentis or Avastin. Both medications are anti-vascular epithelial growth factor therapies that work in similar ways to reduce or prevent abnormal blood vessel growth and leakage. The researchers found no significant associations among the four gene variants and the outcomes that measured the patients' responses to treatment, which were improvement or loss of visual acuity, the status of the retinal anatomy, and the number of medication injections given.

"Our genetic research team remains hopeful that gene variants that predict patient response to AMD treatments will be identified soon," said Dr. Hagstrom. "This would enable a significant leap forward in ophthalmologists' ability to individualize treatment and care plans for their patients."

The findings of the CATT genetic study lend further weight to the American Academy of Ophthalmology's 2012 recommendation on the use of genetic testing. This study assessed the same four major gene variants that are most widely used in current AMD genetic tests and found that the treatment response in patients who carried the gene variants was no better or worse than in patients who did not. The AAO advises against routine genetic testing for AMD and other complex eye disorders until specific treatment or monitoring strategies have been shown in clinical trials to be of benefit to people with specific, risk-linked genotypes.

Altering Rods May Restore Vision

Altering the genetic program of the light-sensing cells of the eye may one day treat some forms of blindness, according to scientists at Washington University School of Medicine in St. Louis.

Working in mice with retinitis pigmentosa, the researchers reprogrammed rods, which enable night vision, making the cells more similar to cones, which sense light in the daytime and detect fine visual details. Doing so prevented degeneration of the retina. The scientists now are conducting additional tests to confirm that the mice can still see.

"We think it may be significantly easier to preserve vision by modifying existing cells in the eye than it would be to introduce new stem cells," says senior author Joseph Corbo, MD, PhD, assistant professor of pathology and immunology. "A diseased retina is not a hospitable environment for transplanting stem cells."

The study is available in the early online edition of *Proceedings of the National Academy of Sciences*.

Mutations in more than 200 genes have been linked to various forms of blindness. Efforts are underway to develop gene therapies for some of these conditions.

Rather than seek treatments tailored to individual mutations, Dr. Corbo hopes to develop therapies that can alleviate many forms of visual impairment. To make that possible, he studies the genetic factors that allow cells in the developing eye to take on the specialized roles necessary for vision.

In retinitis pigmentosa, the rods die first, leaving patients unable to see at night. Daytime vision often remains intact for some time until the cones also die.

Dr. Corbo and others have identified several genes that are active in rods or in cones but not in both types of photoreceptors. He wondered whether turning off a key gene that is activated only in rods could protect the cells from the loss of vision characteristic of retinitis pigmentosa.

'"The question was, when retinitis pigmentosa is caused by a mutation in a protein only active in rods, can we reduce or stop vision loss by making the cells less rod-like?" he explains.

The new study focuses on a protein known as Nrl, which influences development of photoreceptors. Cells that make Nrl become rods, while cells that lack the protein become cones. Turning off the Nrl gene in developing mice leads to a retina packed with cone cells.

To see if this rod-to-cone change was possible in adult mice, Dr. Corbo created a mouse model of retinitis pigmentosa with an Nrl gene that could be switched on and off by scientists.

"In adult mice, switching off Nrl partially converts the rod cells into cone cells," he says. "Several months later, when the mutant mice normally had very little vision left, we tested the function of their retina." The test showed a healthier level of electrical activity in the retinas of mice that lacked Nrl, suggesting that the mice could still see.

Dr. Corbo now is looking for other critical development factors that can help scientists more fully transform adult rods into cones. He notes that if complete conversion of rods to cones were possible, this therapy could also be helpful for conditions where cone cells die first, such as macular degeneration.

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Ophthalmic Product Development Insights

Matthew Chapin and Brian Campion, PhD • Ora Inc., Andover, Mass.

We talk to many ophthalmologists and physician-scientists whose interactions with patients, understanding of clinical practice and therapeutics lead to an "idea." They dream about nurturing the development of that "idea" into an approved therapeutic that can be added to the treatment armamentarium. Invariably, the big question on their minds is "Where do we go from here?"

In this new quarterly column, we plan to showcase and discuss early innovation in ophthalmology. Through a wide variety of case studies we will address the challenges of funding, clinical-regulatory, partnering, intellectual property and other issues facing the physician-scientist and start-up companies. In this issue, we will review key considerations for setting overall product strategy and how this process was implemented by Eye Therapies LLC in bringing their eye-whitening drug concept to a successful global licensing transaction announced a few weeks ago with Bausch + Lomb.

Begin with the End in Mind

To shape and inform the design of the development program, it is paramount to work backwards from the imagined final product. Focusing in this manner on the ultimate product profile goals will help drive specifications for the myriad of interim steps encountered in the journey of development. For an anterior segment drug product, here are some key areas to think about as we break down this complex problem (we will address topics related to other types of products, including devices, drug delivery, and posterior segment in future columns):

• *Mechanism of action.* How does this drug work, and what is the specific disease process that this product will address?

• *Indication & patient population.* What is the exact desired indication and then what aspects need to be built into the clinical program to support desired labeling?

• *Dosing regimen.* What is the expected duration of action and how will frequency of dosing impact potential usage by the patient and physician?

• *Packaging.* What ultimate product presentation to the patient is desirable for the clinician and the patient? (Also considering the feasibility of commercial manufacturing and for some packaging presentations, a simpler form may be more efficient for proof of concept and Phase II).

• *Safety.* Evaluating the risk/benefit profile. Can potential safety issues be mitigated with labeling, patient or physician instructions? Does the prior safety and toxicology information and related pharmacokinetic (PK) support a sufficient safety margin of the locally administered drug for the desired indication? How does the comfort of the product play a role in the specific indication?

• *Formulation/chemistry, manufacturing, controls (CMC).* If possible, many times the best approach for formulation is to keep things simple. However, one may ask, will the addition of other excipients lead to potential product differentiation? How will this impact future work if a formulation change is expected later in development? What shelf life and storage conditions will stability studies support? Should the product be non-preserved or preserved, and how may this impact the options for obtaining proof of concept/Phase II clinical data for the given indication and size of the trials?

The result of the careful consideration of these is a Target Product Profile (TPP) that, if advanced successfully through clinical development and subsequently approved by the Food and Drug Administration for commercialization, would find the highest likelihood of physician and patient acceptance corresponding to the largest available market. It is also critical to assess what metrics need to be achieved after the first studies are completed in order to raise additional funding and/or attract partners. Beyond showing proof of concept for efficacy and safety, this includes ensuring the studies support the ideal dosing that is desired by a partner, including comparative data from an existing drug standard if applicable and defining a product usage pattern. For example is this product meant to be primary therapy, therapy for treatment failures, or will it be used as adjunctive therapy?

Eye Therapies, LLC

The Opportunity. Eye Therapies was started by ophthalmologists Lee Nordan and Jerry Horn, who had identified an unmet need for relieving the common condition of ocular redness in many of their patients. With over 20 million units sold annually, eye redness relief drops are the most frequently used ophthalmic products. Although line extensions around existing active ingredients have been introduced over the years, the currently available products have a short duration of action, lack full efficacy of whitening effect and have issues with rebound and tachyphylaxis. A new active ingredient has not been introduced for this indication for decades. Dr. Horn recognized the opportunity to develop a novel product for redness relief by "re-purposing" a drug approved for glaucoma.

The Team. Dr. Nordan invited Jim McCollum, an experienced pharmaceutical executive, to join as a third partner. This Eye Therapies triumvirate held two key beliefs they felt were critical to the success of the team and the product: 1) the leaders of the company must have invested some of their own funds in the company, and 2) the project needed strong leadership for the clinical-regulatory, medical, and partnering aspects of drug development. Accordingly, they structured Eye Therapies as a capital-efficient, virtual entity and engaged Ora Inc. to manage clinical-regulatory, CMC, product strategy, clinical execution and partnering discussions.

Beginning with the end in mind, it was critical that early in the process there was a structured approach in place to identify and reach out to potential partners and have highly collaborative discussions with them about how the potential product profile can fit into their portofolio. This elucidated the desired target profile of the product to make it an attractive licensing candidate. For this specific product, this included establishment of dose range, comfort, onset and duration of action, comparison to active control, and evaluation for rebound, or tachyphylaxis. These early discussions shaped the TPP. Subsequently,

the early discussions with the FDA provided a forum and the necessary feedback to confirm the design of the intended Phase II program, and impact of the identified metrics on potential labeling.

Eye Therapies successfully raised a "friends and family" round of finance to support advancing the program through a Phase II study designed to validate the key premises of the product profile. After completion of this study, a follow-on meeting with the FDA supported determination of the designs for the remaining Phase II program and confirmed the program was still on track to hit the TPP for the desired labeling.

With the Phase II results in hand that addressed multiple aspects of the TPP, Eye Therapies went on an extensive road show, visiting almost 20 potential partners. Bausch + Lomb ultimately prevailed as their partner, leading to the recent announcement in January of their entering into a global license agreement with Eye Therapies LLC. If approved, the new technology would dramatically expand Bausch + Lomb's potential to compete in the $350 million global ocular redness relief market, and also create opportunity to explore expanded ophthalmic applications.

Eye Therapies successfully built and sold a new product via a capital-efficient, virtual model by "beginning with the end in mind." They established the TPP early by integrating input from the clinician perspective, from working closely with an expert development partner, from engaging in discussions with potential pharma companies and meeting with the FDA to guide decisions on the product profile, and program and clinical design.

The advancement of patient care in ophthalmology is and will continue to be driven by unmet needs and the ability of creative physician-scientists to identify and alleviate those needs through the development of new technologies. The story of Eye Therapies is just the first example on our journey of discussing unique issues in ophthalmic product development. In future columns, we will explore such topics as early financing strategies and other issues related to technical considerations of product development. REVIEW

Mr. Chapin is vice president, corporate development and Dr. Campion is director, business development at Ora Inc. Ora provides a comprehensive range of product development services in ophthalmology.

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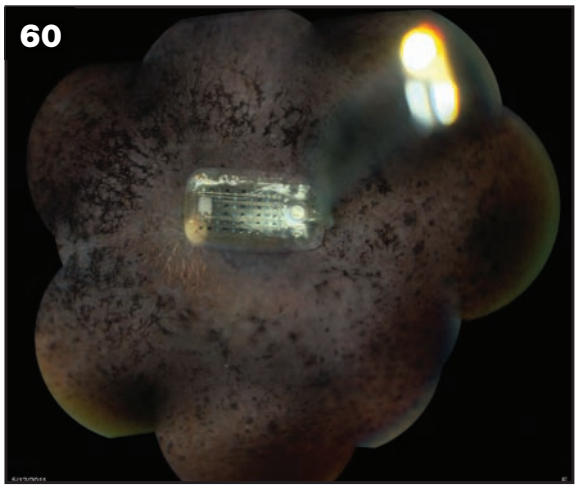

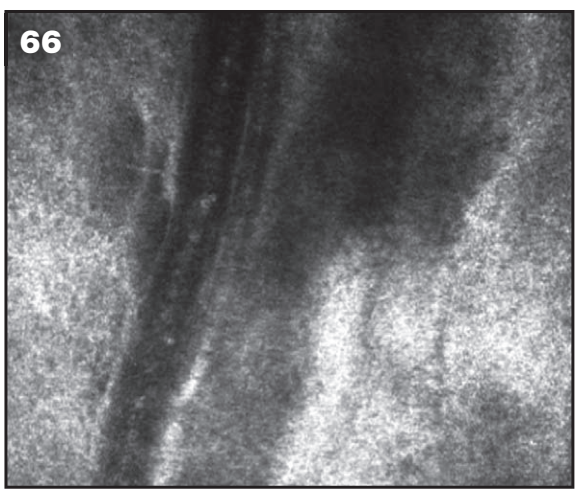

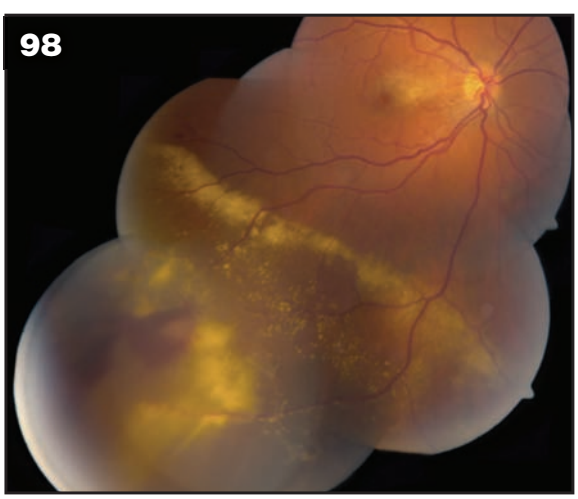

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REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Sight Restored, Vision Still Lacking

Let us begin today by unabashedly celebrating the brilliance of our species. Even as we sit in our living rooms and watch our handiwork doing our bidding on another planet (still an astonishing feat to a child of the '50s who watched Sputnik sail across the night sky), this month we push the boundaries of our achievement even further with the announcement that we can now restore a level of vision to formerly sightless patients. Before today, a child of the '50s would only have encountered such a thing in the Bible.

Specifically, the Argus II retinal prosthesis system from Second Sight Medical received U.S. market approval from the FDA to treat patients with late-stage retinitis pigmentosa *(See Review News, p. 3)*. Second Sight reports that the development of the device benefited from more than $100 million in public investment by the National Eye Institute, the Department of Energy and the National Science Foundation, and an additional $100 million in private investment.

Close on its heels comes the release of peer-reviewed results of Retina Implant AG's ongoing second human clinical trial, published in *The Proceedings of the Royal Society B*. The study examined the results of nine patients blinded by retinitis pigmentosa who were implanted with the company's wireless subretinal microchip. The study found that functional vision was restored for most patients, and visual acuity for two of the nine patients surpassed the visual resolution of the company's first human clinical trial. Patients were followed in and outside of the laboratory and reported the ability to identify facial cues such as smiling, as well as recognize objects such as telephones, red wine versus white wine, door knobs, signs on doors, wastebaskets and more.

We are fortunate to have Sunir Garg on board this month in our Retinal Insider department *(p. 60)*. Dr. Garg provides a detailed look at both technologies, one that couldn't be more timely.

If you've read more than, oh maybe, two of these columns, you probably know that celebrating the brilliance of our species is not my forte. By the time this issue publishes, we may very well be under a federal budget sequestration. (Apparently, with "fiscal cliff" used, they've exhausted the supply of catchy economic disaster names. Sequestration?) There are far more newsworthy and potentially devastating effects among the threatened cuts in funding and jobs that this latest fiscal disaster would trigger. But in this little corner of the world, it could mean a 5.1 percent cut in the budget of the NIH, which played a crucial role in supporting the work we celebrate today.

This species just makes it hard to celebrate.


Getting Meds onto the Eye, 21st Century Style

A new device may ensure accurate medication delivery while reducing the amount of drug needed and monitoring patient use.

Christopher Kent, Senior Editor

Today, the vast majority of ocular medications are delivered as eye drops. Unfortunately, patient use of eye drops is highly imprecise, leading to serious problems with compliance and uncertainty about how much drug is actually reaching the eye.

Now, a new product may offer a way around those concerns. The "Whisper device" is a handheld piezoelectric collimated spray delivery device that uses technology similar to that found in an inkjet printer to get precise quantities of topical medications onto the eye quickly and accurately.

Tsontcho Ianchulev, MD, MPH, clinical associate professor of ophthalmology at the University of California San Francisco, says the company that designed the technology approached him and Mark Packer, MD, FACS, clinical associate professor of ophthalmology at Oregon Health & Science University in Portland, asking for help designing a device that could put this technology to use as a means to deliver ocular medications. "We've been working with them for two or three years to develop this for ophthalmic application," he says.

A New Approach

Dr. Ianchulev says this is completely different from earlier attempts to spray medications onto the eye. "If you just spray a liquid drug toward the eye, the eye will blink, preventing most of the drug from reaching the surface of the eye," he explains. "Second, when you spray aerosols much of the spray evaporates before it reaches the eye. Finally, many spray devices create a turbulent flow that results in a cloud of tiny droplets, so you don't know how much actually reaches the eye.

"This technology solves all of those problems," he says. "It delivers the entire dose of medication in about one-third of the time it takes to blink. So before you can blink, it's already on your eye. It also delivers the drug in a collimated flow—a parallel stream of uniformly sized droplets traveling at the same velocity without much turbulence, as opposed to the cloud of droplets produced by a spray. So, most or all of the medication lands on the eye in the target area."

Dr. Ianchulev says the result is that you can get the same effect from a much smaller quantity of medication, which they were able to demonstrate in a simple study. "We wanted to compare this device to eye drops," he says. "To make the comparison straightforward, we used dilating drops, which cause an easily measureable pharmacodynamic effect. We also tried using far smaller quantities of the drug to see whether the effect would be the same."

For the study, more than

All images: Tsontcho Ianchulev, MD, MPH

Using technology like that found in inkjet printers, the Whisper device gets liquid medications onto the eye accurately and so quickly that the meds are delivered before the person can blink.

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1. LASTACAFT® Prescribing Information. **2.** Torkildsen G, Shedden A. The safety and efficacy of alcaftadine 0.25% ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. *Curr Med Res Opin.* 2011;27(3):623-631. **3.** Data on file, Allergan, Inc., 2005.

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200 eyes of more than 100 patients were randomized. "One eye received the medication via eye drops, which put about 30 µl onto the eye," he explains. "The other eye received either 1.5 µl, 2 x 3 µl, or 6 µl of the drug delivered with the Whisper device. With digital pupillometry we found that the pupils dilated equally rapidly, and dilated the same amount. There were no significant differences between the eye dropper and the Whisper device—even when the amount of drug delivered was a tiny fraction of the amount being delivered by the eye dropper. Essentially, 6 µl of drug delivered by the Whisper created the same dilation effect as about 30 µl delivered via an eye drop."

The Whisper device has an LED targeting circle that allows the patient to center the device directly in front of the cornea. No head tilting is required.

Other Considerations

The device consists of a base that contains replaceable batteries and a top section that contains a given medication. "When you get a new medication, you replace the top cartridge," explains Dr. Ianchulev. "Once you've used it for a year or so, you simply replace the batteries in the base." To ensure accurate targeting, the new device has a small LED targeting circle that allows the patient to center the device right in front of the cornea. (*See above.*)

The designers say that using the device is comfortable for the patient. "The one thing we did not include in our presentation of the data was that we gave the patients a questionnaire asking which approach they liked better, in terms of user-friendliness," notes Dr. Ianchulev. "Ninety-two percent of the subjects favored the Whisper device."

Dr. Packer confirms this. "When I first used a prototype device a couple of years ago, I was astonished," he says. "The micro droplets are ejected with the touch of a button. I barely felt anything contact my eye; there was no stinging, burning or tearing."

Regarding preservative exposure, the device offers three advantages, according to Dr. Ianchulev. "First, if you can put 3 to 6 µl of drug on the eye instead of 30, you're cutting the amount of preservative exposure by a factor of five or 10," he says. "Second, the device has multiple seals that maintain sterility, meaning there's less need for a preservative. Third, the patient is very unlikely to touch his eye with the device."

Dr. Ianchulev notes that the company has successfully used the device with more than 90 different ophthalmic medications to date. "That covers most of the medications out there," he says. Even the more difficult ones such as Restasis, which is a very viscous, non-Newtonian fluid, worked. That means the technology is widely useable, and also indicates that companies can deliver the formulations that are currently approved; they'll just be packaging them differently. We believe this will be critical to adoption by pharmaceutical companies."

Clearly, this technology will be somewhat more costly than a simple eye dropper bottle, but Dr. Ianchulev notes that this will be offset by the need for smaller quantities of the drug. "There will be minimal additional expense to the pharmacy or consumer beyond the current price of the topical medications themselves," he says. "When you have a drug that costs $50 or $60 a month, and this allows you to get a lot more out of it at a lower dose, it's commercially quite compelling."

The device can also digitally track usage. "These devices are being designed with a little chip that can communicate directly with your computer or iPhone," says Dr. Ianchulev. "The chip monitors how many times you use the spray per day."

"The device can even remind you when your dose is due," adds Dr. Packer. "In addition, the Whisper device can be designed to provide a summary of your compliance to you and your doctor over the Internet."

Currently, they're working to establish the safety and effectiveness of the device for delivering multidose preservative-free agents. "The initial work that's been done holds promise," says Dr. Packer, "but there is much left to do in this arena."

Coming Soon

Dr. Ianchulev believes the device will most likely be commercially available first outside the United States. "I think it will start out delivering dry-eye products such as artificial tears," he says, "and maybe some clinic-based applications such as steroids. Eventually it could be used to deliver glaucoma drops. Hopefully approval in the U.S. will happen fairly quickly because there's very little safety risk and a lot of benefit."

"The benefits of this device should be enormous," says Dr. Packer. "Those patients with the dual diagnoses of glaucoma and ocular surface disease, in particular, will enjoy better compliance with fewer side effects." REVIEW

Drs. Ianchulev and Packer are directors of Corinthian Ophthalmic Inc., manufacturer of the Whisper device, and own equity in the company.

Cataract Patients: Younger Every Year

Christopher Kent, Senior Editor

The trend toward cataract surgery at ever-younger ages brings with it new challenges and rewards. Here's help making the most of it.

There's no question that cataract surgery—once put off as long as possible and largely reserved for elderly patients—is now being performed on many people who have not even reached retirement age. Here, four experienced surgeons talk about the reasons for this shift, how it has affected their practices and approaches to the patient, and what surgeons can do to most effectively meet the needs of these younger individuals.

Why the Shift?

"I think there are several factors that account for this demographic shift," says Stephen S. Lane, MD, medical director at Associated Eye Care in St. Paul, Minn., and adjunct professor of ophthalmology at the University of Minnesota. "First, the baby boomer generation that's now turning 65 has a greater awareness and knowledge of cataract surgery, partly because of the computer and partly because of peer-to-peer interactions spreading awareness of the trend. Second, the surgery is safer and our overall results are better because of improvements in technology, including the IOLs we implant, our measuring technology and the surgical instrumentation we now use. Third, I think we're now dealing with cataract surgery as a refractive procedure. We've given a lot of lip service to this idea in the past, but today we really are able to treat cataract surgery as a refractive procedure. And I think it will continue to get better."

"There are many reasons for the shift toward younger cataract patients," says Stephen Slade, MD, FACS, who practices at Slade & Baker Vision Center in Houston. "One is that the surgery has changed. When I started training 25 years ago, people would be in the hospital for two or three days to have a cataract removed; they couldn't move around and it would take a while to get their vision back. So, they were told to postpone the surgery until the cataracts got really bad. Today, the surgery has gotten much easier; there are far fewer complications and much less fear, and the technology has improved dramatically. The surgery has become much more of a procedure and less of an operation."

"The technology is better than in the past—and surgical expectations are also higher," notes Samuel Masket, MD, clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA School of Medicine. "Together, these factors have helped to increase the volume of surgery in

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younger-age individuals. But perhaps the most significant factor in this shift is the aging of the baby boomers, who are now turning 65 in large numbers. This is the same group of individuals who sought the technological advances of laser vision correction, attempting to improve their quality of life. Now they're seeking to take advantage of the latest advances in cataract surgery."

Dr. Slade points out that the shift has been accompanied by a change in the definition of lens "dysfunction." "Essentially, you have cataract surgery because the lens stops working," he says. "In the past, 'stops working' was defined as 'the lens gets cloudy.' But in reality a healthy lens also focuses the light for both distance and near, and the lens stops doing that around the age of 40."

A Different Generation

This shift to younger cataract patients is leading to changes in the doctor's office as well, and much of that is attributable to generational differences. "Baby boomers are not their parents," notes Dr. Slade. "The previous generation was more complacent—they expected less. I'm a baby boomer myself, so I can say this: There's nobody as whiny as a baby boomer. One little thing wrong and baby boomers want to have it fixed. And they're used to having it fixed—whether the 'fix' is Botox or Restylane or Viagra or wrinkle cream, or having a hip or knee replaced. Baby boomers are actively looking for solutions, where the previous generation was passively hoping for solutions."

"People who are in the next generation older typically accept that with age comes loss of opportunity, loss of function," observes Dr. Masket. "The baby boomers don't adhere to that philosophy. So, when they sense they have any type of limitation in their vision, they want it fixed. And the fact that we can now come closer to meeting those expectations than we could in the past supports their desire to get this problem addressed earlier."

"Younger patients are accustomed to paying out-of-pocket for health-care related expenses. The more elderly patients are not used to spending disposable income for lifestyle advantages through medical procedures."
—Samuel Masket, MD

"Another difference is in their level of knowledge about the surgery," adds Dr. Slade. "People go on the Internet now and learn more about cataract surgery in 20 minutes than most first-year ophthalmology residents learned in six months 20 years ago. And, the surgery is now able to address problems like high myopia, hyperopia, astigmatism and even presbyopia. The improvements in cataract surgery fit very well with the baby boomers' desire to get things fixed as soon as they become an issue."

Another difference between the generations may be their attitudes regarding spending money for optional procedures. "One part of that is that younger patients are accustomed to paying out-of-pocket for health-care related expenses," says Dr. Masket. "These are people who have paid out-of-pocket for procedures like LASIK or Botox, to get what they perceive to be a better look or better lifestyle. The more elderly patients are not used to spending disposable income for lifestyle advantages through medical procedures. It's a little bit foreign to them. In fact, as more young cataract patients come into our offices, it makes increasing sense to offer these options because this group of individuals has already demonstrated their willingness to pay for procedures."

Boomers and Technology

Another difference in the attitudes of baby boomers, noted by many surgeons, is their interest in trying cutting-edge technology. "It's rare in my practice for anyone over the age of 80 to be interested in premium IOLs," notes Richard L. Lindstrom, MD, founder and attending surgeon of Minnesota Eye Consultants and adjunct professor emeritus at the University of Minnesota Department of Ophthalmology. "Patients over 80 prefer to wear glasses. The younger patients are more interested in refractive cataract surgery."

Despite this trend, Dr. Slade says he doesn't necessarily recommend presbyopia-correcting IOLs more often to younger cataract patients than older ones. "Whether the patient is 45 or 85, when you take a cataract out you have created absolute presbyopia if you put in a monofocal, regardless of age," he notes.

Dr. Masket agrees, noting that some people over the age of 75 or 80 may still be open to advanced technology. "You have to individualize," he says. "There's no blanket rule to apply here. But when you look at trends, clearly the trend is toward baby boomers spending more on lifestyle enhancement."

In fact, Dr. Slade believes that advanced technology such as premium IOLs could be of significant benefit to elderly patients. "It's possible that younger patients who are still in the workforce might be better able

to afford them, and they're probably more active than older patients," he continues. "However, I think that's balanced by the fact that the older you get, the smaller your world is—the more you tend to read, watch TV, stay inside. In other words, I don't think you can argue that having good near and distance vision become less important to you as you age. You're more dependent on your vision for both safety and entertainment. If you're young and you stumble, you'll probably recover and you won't break anything. If you're older, it's a whole different thing to fall and break your hip. And older individuals who are still employed are probably more likely to have a job that depends on their eyesight. So I think your vision becomes more vital to you in just about every way as you get older."

Dr. Masket notes that the baby boomers' interest in cutting-edge technology may also extend to femtosecond cataract surgery. "Although it's not yet clear whether using the femtosecond laser improves optical outcomes, I would say that more of my patients below the age of 65 or 70 opt to pay for femtosecond laser-assisted surgery," he says. "I happen to practice in a wealthy demographic where some of the older people I care for have far more money than some of the younger people, so I don't believe it has anything to do with that. I think it's all about mindset."

Surgery on Younger Eyes

For some surgeons, dealing with an increasing number of younger eyes makes a difference in the operating room as well. "Some younger patients who haven't undergone surgery are a little more anxious, compared to older patients who have been through more surgery in the course of their lives," notes Stephen S. Lane, MD, medical director at Associated Eye Care in St. Paul, Minn. "They have more questions than older patients who have often seen multiple doctors over the years. You have to be patient, answer their questions and make sure they're comfortable with the procedure.

"Intraoperatively, more anti-anxiety medications or anesthesia may be necessary for a younger person than an older person," he adds. "They tend to be healthier, so it's usually safer for them to receive a little bit more medication. In general, it takes a little bit more TLC to achieve the same sort of comfort level with a younger, less surgically experienced patient."

Stephen Slade, MD, FACS, who practices at Slade & Baker Vision Center in Houston, notes that younger eyes are easier to operate on. "The cataracts are softer, there's less phaco time, they heal better, the corneas are generally clearer and the pupils dilate better," he points out. "The eyes are usually healthier, and there are fewer other things going on." (Richard L. Lindstrom, MD, founder and attending surgeon of Minnesota Eye Consultants, notes that the prevalence of softer lenses in these patients causes him to favor supracapsular phaco.)

Samuel Masket, MD, clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA School of Medicine, says his surgical protocol has shifted in order to meet these heightened baby boomer expectations. "I now incorporate intraoperative aberrometry for all normal eyes, not just the outliers or post-LASIK eyes or eyes in difficult situations," he says. "Using intraoperative aberrometry, I end up changing the lens power in 43 percent of cases. As a result, we're now within 0.5 D of our goal in about 90 percent of eyes. For the younger patients this is probably the most important thing—along with having a non-complicated procedure. Even at this level, we still encounter patients who are disappointed that they're a half-diopter off.

"Another thing I do now, especially in the younger individual, is remove the subcapsular lens epithelial cells under the anterior capsule to the greatest extent I can," he adds. "This reduces the fibrotic change and capsule phymosis that is especially common in younger people. There are numerous long-term advantages to doing this, although it does add more time to the chair discussion and in the operating room."

—CK

Boomer Expectations

One important difference in the baby-boomer generation noted by surgeons is higher expectations than previous generations. "If you tell a baby boomer he has to wait five minutes, he'll try to figure out a way to cut it to three minutes," notes Dr. Slade. "If you tell him to sit in row eight, he'll try to sit in row four. Boomers have high expectations for eye surgery, and right now we're really not able to meet all of those expectations.

"The other problem," he adds, "is that these patients often have no expectation of a negative result. If a younger, clearer-lens patient has a significant complication such as an infection or vitreous loss, it's hard for him to accept it, no matter how well he's counseled before surgery."

Dr. Slade says you have to see this problem coming and deal with it up front. "It's important to make sure you really get in the patient's face and emphasize that although this is a very low-risk surgery, it is surgery, and there are risks," he says. "Sometimes you emphasize this to patients and they say, 'I know that will never happen to me.' Or, 'That's why I came to you—I know you're the world's greatest doctor. You never have a complication.' In that situation you have to say, 'Thank you, but that's not correct.' And sometimes you have to be willing to say, 'I just don't think this is a good option for you right now because of your expectations.'

"It has a lot to do with the risk/benefit ratio," he adds. "One of the

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scariest phone calls I ever had was from a surgeon who had done bilateral ICLs on a 7- or 8-D myopic patient, both on the same day. The patient came back a few days later with infections in both eyes. If something does go wrong with an early cataract patient, you have a serious problem; you weren't saving his vision, you were removing an inconvenience. You have to be prepared to deal with that possibility and make the patient understand at the outset that his expectations really need to be realistic."

Dr. Lane agrees. "On average, the younger population is more demanding and they won't be satisfied with their vision unless it meets their expectations," he says, "so I think it's really important to clearly define what those expectations should be.

"To help convey the risks associated with these procedures our practice uses visual aids, and we have these patients spend time with counselors that we've trained," he adds. "Still, it's one thing to say something to the patient; it's another thing for the patient to grasp what you're saying. You have to make sure your patients understand that complications can happen to anybody—including them."

The Previous-LASIK Factor

Dr. Lane notes that many of the current, younger cataract patients have previously had refractive surgery such as LASIK or PRK. "They know the kind of results they can get," he points out. "Now, as they turn a little bit older, they start to develop early cataracts. Ten years ago we might have said, 'Come back in a year or two and we'll see how that cataract is coming along.'

"That level of vision isn't satisfactory to these patients," he continues. "Today's younger cataract patients are more likely to say, 'No, this is really bothering me. I can't live with this for another year or two. And I know you can get good results with today's lenses and technology because I've been reading about it. I'm going to need cataract surgery in several years anyway, so let's do it now.' I also think this generation is less afraid of surgery than their parents were—and for good reason. The surgery is safer and complications are fewer."

"Patients who have previously had LASIK have become used to a certain level of vision. When that becomes impaired they want it fixed, and back to the level it was at before it got broken. So if they had a good LASIK result and now have to wear reading glasses and are getting a cataract, they're going to want lenses that can correct for both distance and near."
—Stephen Lane, MD

Dr. Slade agrees that previous LASIK is an issue. "If they've had it and it turned out well, you have a problem because you don't have anything quite as dramatic to offer them—unless they have a true cataract," he says. "If you take them from cloudy to clear vision, that's something."

"Patients who have previously had LASIK have become used to a certain level of vision," adds Dr. Lane. "When that becomes impaired they want it fixed, and back to the level it was at before it got broken. So if they had a good LASIK result and now have to wear reading glasses and are getting a cataract, they're going to want lenses that can correct for both distance and near. It's a progression: going from glasses to contact lenses to LASIK to refractive cataract surgery. So I spend more time talking with the younger patients about the options that allow them to remain free of glasses—especially LASIK patients who come to see me with early cataracts."

Dr. Masket agrees that expectations are elevated when patients have previously had LASIK. "We know from published studies that typically 93 percent of the LASIK population will come within 0.5 D of their optical goal," he points out. "Whereas, looking at the cataract literature, using the National Health System in the U.K. as an example, their published rates for cataract surgery are 55 percent within 0.5 D of the optical goal and 85 percent within 1 D. The problem is that the younger patients are expecting the level of optical result achievable with LASIK. In addition, they expect the surgery to be painless, nearly instantaneous and cosmetically nonblemishing. LASIK has really changed the way people think about eyes and eye surgery. This is this mindset we have to deal with."

Dr. Lane points out that, ironically, previous LASIK can undermine the advantages of current presbyopia-correcting technology. "Previous LASIK makes the outcome less predictable," he notes. "So this becomes part of the expectation issue. Patients who have had LASIK need to understand that sharpness of vision after cataract surgery may not be as good as it would have been if they had not had LASIK 20 years earlier. That's especially true if the LASIK was done with one of the older lasers."

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CNS Depressants: Although specific drug interaction studies have not been conducted with ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Tricyclic Antidepressants: Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with ALPHAGAN® P in humans can lead to resulting interference with the IOP-lowering effect. Caution is advised in patients taking tricyclic antidepressants, which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors: Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side effect such as hypotension. Caution is advised in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

ADVERSE REACTIONS

Adverse reactions occurring in approximately 10% to 20% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5% to 9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Please see the Brief Summary of the full Prescribing Information on the next page.

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Alphagan P 0.1%
(brimonidine tartrate ophthalmic solution) 0.1%

ALPHAGAN® P

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(brimonidine tartrate ophthalmic solution)
0.1% and 0.15%

BRIEF SUMMARY

Please see **ALPHAGAN® P** package insert for full prescribing information.

INDICATIONS AND USAGE

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15% is an alpha adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Neonates and Infants (under the age of 2 years)
ALPHAGAN® P is contraindicated in neonates and infants (under the age of 2 years).

Hypersensitivity Reactions
ALPHAGAN® P is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

Potentiation of Vascular Insufficiency
ALPHAGAN® P may potentiate syndromes associated with vascular insufficiency.

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Severe Cardiovascular Disease
Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

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**).

ADVERSE REACTIONS

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

Adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse reactions occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following reactions were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

Postmarketing Experience
The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia. Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides
Because **ALPHAGAN® P** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN® P** is advised.

CNS Depressants
Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Tricyclic Antidepressants
Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors
Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category B: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg /kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively, than similar values estimated in humans treated with **ALPHAGAN® P** 0.1% or 0.15%, 1 drop in both eyes three times daily.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **ALPHAGAN® P** 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
ALPHAGAN® P is contraindicated in children under the age of 2 years (see **CONTRAINDICATIONS**). During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

Special Populations
ALPHAGAN® P has not been studied in patients with hepatic impairment.

ALPHAGAN® P has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

OVERDOSAGE

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse reaction reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving **ALPHAGAN® P** as part of medical treatment of congenital glaucoma or by accidental oral ingestion (see **USE IN SPECIFIC POPULATIONS**). Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **ALPHAGAN® P** 0.1% or 0.15% into both eyes 3 times per day, the recommended daily human dose.

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro and in vivo studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three in vivo studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 and 90 times the systemic exposure following the maximum recommended human ophthalmic dose of **ALPHAGAN® P** 0.1% or 0.15%, respectively.

PATIENT COUNSELING INFORMATION

Patients should 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**). Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Patients also should 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.

As with other similar medications, **ALPHAGAN® P** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Rx Only

Revised: 11/2011

Based on package insert 71816US15C

APC57BC13

Alphagan® P 0.1%
(brimonidine tartrate ophthalmic solution) 0.1%

Making the Best of It

Treating younger cataract patients means new challenges and opportunities. "These patients are more demanding," notes Dr. Lindstrom. "They want a high tech/high touch experience. They will check out the surgeon and share their experience widely, including on social media." Surgeons offer the following suggestions to increase the likelihood of a positive experience for you and your younger cataract patients.

• ***Think long-term.*** Dr. Masket notes that when operating on a younger cataract patient the post-surgery lifespan is considerably greater. "When we do a procedure, there's more at stake than how the patient will see over the next three months," he points out. "With younger people, we have a long-term obligation.

"At one time I was doing a relatively large number of pediatric cataracts," he says. "It was daunting to realize that the quality of my work had to last for 90 years. Now, as we operate on cataract patients who are getting younger, our work may have to last for 40 or 50 years. So it's a significant decision regarding which lens might serve the patient best over the course of a lifetime. That means, for example, that if we're considering implanting multifocals, we need to consider whether there's a strong family history of macular degeneration or other condition that may limit quality of vision as the patient ages.

"We really need to do our best-case procedure with young individuals," he adds, "because our responsibility goes up as the patient's age goes down."

• ***Keep your website up-to-date.*** "Your website needs to be excellent and informative, and ranked high so that it comes up when patients Google your name," notes Dr. Slade.

• ***Provide work-friendly time slots.*** "It's important to deliver the kind of patient experience that will meet the busy, active lifestyles of this group of patients," says Dr. Lane. "They're not going to patiently sit in your waiting room for an hour and a half waiting for their appointment.

"This is a generation that's used to having things done simply, quickly and exactly," he continues. "You might want to set aside specific times in your schedule for these patients. For example, you could make earlier time slots available so they can come in, get done and get to their office at the start of the day, or make slots available at the end of the day after work."

• ***Allow more chair time.*** "I like to say that it used to be very easy to do cataract surgery," says Dr. Masket. "We had very few lenses to choose among, in terms of their function—just materials and design. We didn't have toric lenses or presbyopic lenses. We didn't have lasers or aberrometry. The fact that we have so much more technology to offer translates to increased chair time. Patients must be cognizant of the benefits and drawbacks of all of these new lenses and devices.

"To accommodate this, we try to schedule cataract consult time when we are primarily seeing only these patients, rather than mixing them in with other case types—for example, blepharitis, conjunctivitis or glaucoma management patients," he says. "In these blocks we're scheduling fewer patients and giving them more time, but the economics pan out because many of the patients choose shared-expense options."

• ***Make sure your office looks modern.*** "The practice needs to look good cosmetically," notes Dr. Slade. "People used to expect a tiny waiting room with a glass window that slid open when you rang the little bell. Now they have more modern ideas of how a practice is supposed to look."

• ***Consider having designated technical staff or check-in staff for these patients.*** "Make sure your counselors understand that these patients have higher expectations and are likely to want in-depth education about the procedure," suggests Dr. Slade.

• ***Make the waiting area fit their lifestyle.*** "Think about the choice of magazines you have in the waiting room and the type of coffee you serve," says Dr. Lane. "You can provide iPads and other high-tech devices for them while they're waiting. We have Internet service in our office so patients can access the Internet on their iPads or smartphones. Those inds of things are all geared to this younger cataract population."

• ***Take cosmesis into account.*** "Many younger patients are concerned about the cosmetic aspects of the surgery," advises Dr. Masket. "Certain lenses generate increased Purkinje images. We try to be sensitive to this, and if the patient is concerned about it, we may choose a lens that's less likely to create Purkinje images."

• ***Offer financing for out-of-pocket options.*** "Younger patients are likely to have more disposable income," notes Dr. Lane. "They're used to reaching into their pocket and paying for things. They aren't nearly as conscious, for example, about what insurance does and doesn't cover. They have many work years left ahead of them, and that seems to make them feel that they can afford to spend money.

"Older patients, even if they have disposable income, seem to be more concerned about whether they have enough money," he continues. "They're not working, so their savings are slowly dwindling. Some feel that they're broke even though they have hundreds of thousands of dollars in the bank. Meanwhile, the younger generation is borrowing money to buy the latest car without any money in the bank.

"These are generalizations, of course, but I think older patients are

generally more concerned about finances," he adds. "The younger generation is also more accustomed to borrowing money. They'll often finance a procedure such as LASIK, which is much less common in the older generation of patients. So I think it's important to offer financing options for premium alternatives. I think you need to treat these younger cataract patients as if they were LASIK patients."

• ***Maintain the vision the patient is accustomed to.*** "We don't want to convert people who have had laser vision and are free from glasses to people who are dependent on glasses," notes Dr. Masket. "So if they've had a strategy that has worked well for them, I try to do the same thing in the selection of IOLs. If they're accustomed to monovision, we'll continue them in monovision. If they've worn contact lenses that correct for astigmatism, we'll try to match that. Above all, spectacle independence is a very important consideration when dealing with the younger age group. As a group they've demonstrated their desire to be spectacle-free."

How Far Might This Go?

Given the trend toward cataract surgery at an earlier age, what is the logical endpoint? "As the outcomes of cataract surgery improve, I think the age of patients who will want to have this is going to continue to go down," says Dr. Lane. "Cataract surgery, regardless of the density of the cataract and the disability involved, is still an elective procedure. So the better the results and the faster the rehabilitation, the more people are going to demand this, and the earlier they'll want it. Fifteen years ago we never dreamed of doing cataract surgery on a patient with 20/25 vision. Now it's not uncommon."

"It's very disabling to lose your near vision," notes Dr. Slade. "Ideally, people would like to treat that. At this point, I think the surgery is almost ready to meet that need, but the lenses aren't quite there yet for everyone.

"We have some things to accomplish before we can offer lens-based surgery as a refractive tool to everybody. We really need to control the fate of the capsular bag and the subcapsular lens epithelial cells; we need to have a greater degree of accuracy in our optical outcomes; and we need to address the issue of true and adequate accommodation."
—Samuel Masket, MD

"The presbyopia-correcting IOLs are way better than anything we had 10 years ago, but they're not perfect," he adds. "However, if the lenses get better, then I think it will really become the norm. People are willing to have a face lift for saggy skin and botulinum toxin injected into their faces, so I think people will be willing to have a very safe procedure to get their full range of vision back."

Dr. Masket notes that obstacles to early surgery for presbyopia remain. "We have some things to accomplish before we can offer lens-based surgery as a refractive tool to everybody," he says. "We really need to control the fate of the capsular bag and the subcapsular lens epithelial cells; we need to have a greater degree of accuracy in our optical outcomes; and we need to address the issue of true and adequate accommodation. In the absence of those considerations, I don't see this trend toward younger cataract patients going much further at this point.

"Of course, those issues will eventually be addressed," he continues. "I'm often amazed that despite the constraints of the marketplace, the constraints of the Centers for Medicare & Medicaid Services and the constraints of the FDA, manufacturers keep investing in R&D. We continue to have more products available to us. Technology will improve, and as it improves, utilization will go up. That's been demonstrated many times.

"Presbyopia is one of the most unpleasant conditions for people to accept," he adds. "It comes right around the time a lot of people are dealing with midlife crisis, so there surely is an emotional component to it; it's more than just an annoyance. Presbyopia reminds us of our mortality and interferes with our lifestyle. So when we have better presbyopia solutions, from the standpoint of lens-based surgery, there's no question that they will be adopted at any early age."

"Surgery will keep getting done earlier for many more decades," agrees Dr. Lindstrom. " 'Dysfunctional lens syndrome' is the cataract of the future. Presbyopia and reduced contrast sensitivity will be the indication someday."

"All things considered, I could easily see the day when 90 percent of people get their lenses swapped out between the ages of 40 and 45," adds Dr. Slade. "If the surgery is that safe and effective, why wouldn't they?" REVIEW

Drs. Masket, Lane, Lindstrom and Slade consult for Alcon and Bausch + Lomb; Drs. Lane and Lindstrom also consult for Abbott Medical Optics; and Dr. Slade also consults for IntraLase.

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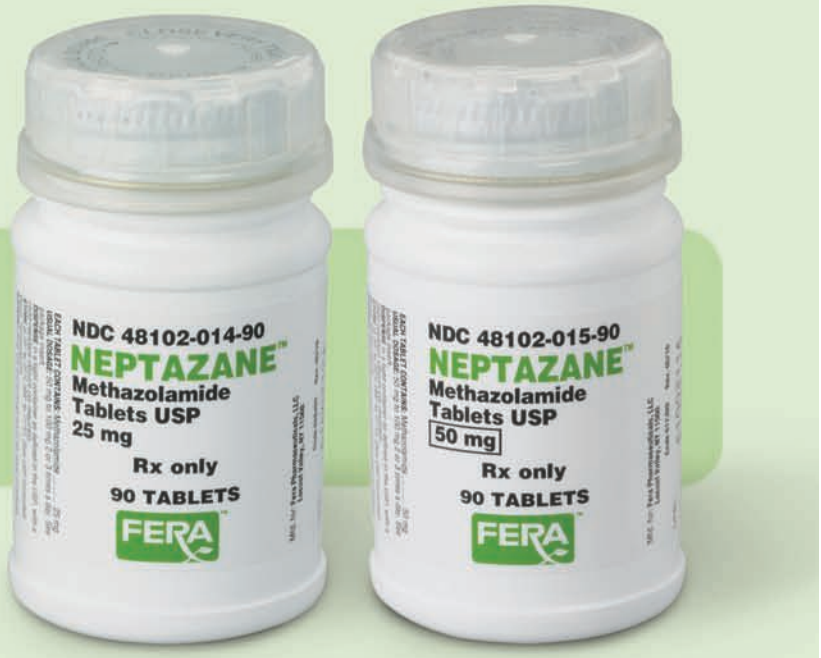

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How to Know When Less is More

Walter Bethke, Managing Editor

Surgeons say that the best procedure for some glaucoma patients is cataract surgery—but the trick is choosing the right patients.

In addition to being a sophisticated, highly efficient way to restore a patient's sight, cataract surgery can also work its magic on certain glaucoma patients by lowering their intraocular pressure without the need for an adjunctive glaucoma procedure. Glaucoma experts say, however, that the key is discerning which glaucoma patients will benefit from cataract surgery alone and which will require a combined procedure. Telling the two groups apart isn't always easy, but if you're able to, you can spare these patients the risks of a second procedure while still enjoying the benefits of lower pressures. In this article, surgeons share their techniques for identifying the patients most likely to benefit from cataract surgery alone.

Cataract Surgery's Benefits

Surgeons say that studies have found a very real benefit from cataract surgery in certain fortunate glaucoma patients.

In one study with 10 years of follow-up, surgeons analyzed the final intraocular pressure reduction in five groups of cataract-surgery patients (124 eyes), segmented by preop IOP levels. They found that the higher the preop IOP, the more pronounced the postop IOP decrease was. The final mean IOP reduction was 8.5 mmHg (34 percent) in the 29 to 23 mmHg preop IOP group, 4.6 mm Hg (22 percent) in the 22 to 20 mmHg group, 3.4 mmHg (18 percent) in the 19 to 18 mmHg group, and 1.1 mmHg (10 percent) in the 17 to 15 mmHg group. In the 14 to 5 mmHg preop IOP group, IOP actually increased by 1.7 mmHg (15 percent). Though other studies have found varying durations of this IOP decrease, usually a couple of years, in this particular study the one-year IOP reductions persisted for 10 years and didn't differ by age. The researchers concluded that the aging crystalline lens may be a significant cause of ocular hypertension and glaucoma, and that phaco may help prevent and treat glaucoma.[1]

In a more recent, retrospective study of 60 primary angle-closure glaucoma patients, the researchers looked at the effect of phaco. They found that the mean IOP after cataract surgery decreased significantly (4.5 mmHg, $p<0.01$). Also, 20 percent of the patients were able to discontinue antiglaucoma medication after surgery. They say the change in IOP didn't correlate with lens thickness or anterior chamber depth.[2]

In addition to direct health benefits, performing cataract surgery alone may have clinical benefits, as well. "I'm a

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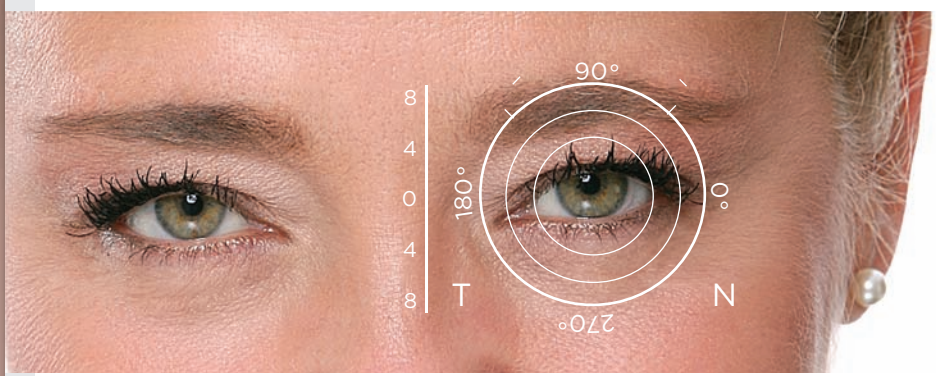

Resolving Post Cataract Astigmatism:

Evaluating the Options

Speakers:

Eric Donnenfeld, MD, FACS
Ophthalmologist - Corneal, Cataract & Refractive Surgery
Ophthalmic Consultants of Long Island

Steven Schallhorn, MD
Global Medical Director for Optical Express

Objectives:

» Post Cataract Astigmatism and Patient Satisfaction
» Growing Incidence and Patient Identification
» Understanding Manual and Laser Arcuate Incisions
» Differentiation of Laser Platforms
» Cases Best Suited for a Toric Lens
» Managing Astigmatism Post Cataract in Your Practice
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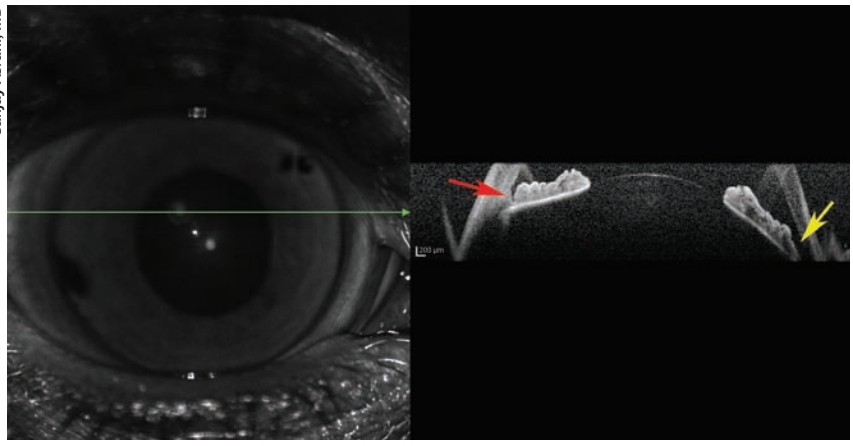
Sanjay Asrani, MD



Anterior segment optical coherence tomography can be helpful preop. Here, the red arrow highlights anterior synechiae, and the yellow shows where the angle is narrow but still open, in a case of phacomorphic glaucoma.

proponent of doing cataract surgery, because it makes all of our diagnostic testing better postoperatively," explains Fairfield, Conn., glaucoma specialist Robert Noecker. "Sometimes, when the cataract is in the way, you can get a bad signal and you can't always take things at face value. For example, visual fields may be unsatisfactory because of the interference of the cataract. But when the cataract is out, it helps your future evaluation of the patient."

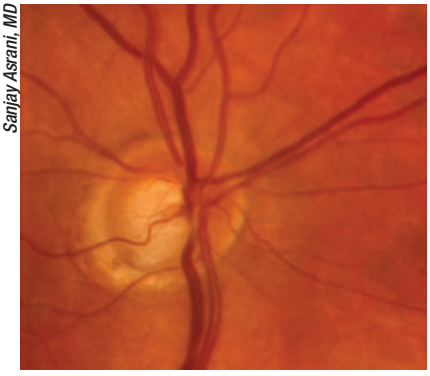
Choosing Patients Wisely

Physicians say determining which patient might benefit from cataract surgery alone involves putting together a gestalt of information from the medical history, medication use, imaging and the physical exam. Here are the main areas to focus on:

• ***Number of medications.*** "Those patients on zero, one or maybe even two glaucoma medications are likely to do better with cataract surgery alone than someone on maximum medical therapy," says Yale glaucoma specialist James Tsai, MD. "If a patient is on three or four classes of glaucoma medications—and I count Combigan or Cosopt each as two classes—I'll consider combined surgery instead."

• ***Examine the angle.*** Gonioscopy, which some surgeons say is a lost art, reveals a lot of pertinent information, surgeons say. "Gonioscopy shows us that, if the patient has already had a laser iridotomy and his angle is very narrow or almost closed despite the iridotomy, there's a good chance that his cataract is contributing to the glaucoma," says Duke University glaucoma specialist Sanjay Asrani, MD. Surgeons recommend using a four-mirror handheld lens so compression can be performed. "When I do gonioscopy, I note whether I'm able to compress the eye easily to open the angle with the goniolens," Dr. Asrani says. "If I'm unable to compress easily, it's likely that the agent that's not allowing me to compress is actually the cataract. If I'm able to compress easily, then most likely the narrow angle is from pupillary block—meaning a fluid cushion that I'm able to easily compress and open up the angle. Note that if a patient has already had a laser iridotomy, he shouldn't have pupillary block.

Sanjay Asrani, MD



The optic nerve exam can help determine if a patient needs a combined procedure. Here, the damage is in the inferior pole.

"The other feature I examine is the pigmentation in the trabecular meshwork," Dr. Asrani continues. "If the pigmentation is pockmarked, then it's likely that the iris has butted up against the trabecular meshwork and left extra pigmentation in those areas, leading to spotty pigmentation. Many patients with coexisting cataract and glaucoma have a narrow-angle component, so the challenge is to identify it, doing gonioscopy carefully in a low level of light, not crossing the pupil and understanding that you shouldn't assess the angle as soon as you put on the goniolens, but instead 10 to 15 seconds later. You have to wait for pupillary block to recur during gonioscopy in order to assess the true nature of the angle."

Gonioscopy also helps in other patient presentations, as well. "Gonioscopy can help discern if the patient has narrow angles and/or a plateau iris configuration, since these conditions may improve with removal of the lens," explains Dr. Tsai. "One may also look to see if there is traumatic angle recession, a type of glaucoma in which removal of the lens will not likely help. Gonioscopy can also give clues as to how much pigment deposition is in the trabecular meshwork and if there are any peripheral anterior synechiae or signs of angle-closure due to trauma. However, gonioscopy isn't likely to predict who will benefit from cataract surgery alone, because, for instance, we can't see microscopically how much debris is in the trabecular meshwork."

If synechiae are present, it doesn't bode well. "If there are areas of synechiae between the iris and trabecular meshwork, that tells me that the apposition between the trabecular mesh-

work and the iris has been present for quite some time," explains Dr. Asrani. "The meshwork in those areas is not functioning. Large areas of synechiae lead me to believe that the cataract surgery alone won't have a significant effect by itself."

Dr. Noecker says ultrasound can be very helpful when assessing the anterior segment. "I think it's definitive," he says. "Though anterior segment OCT is less-invasive, and can give you an idea of the angle contour, it's limited by the front side of the iris. With UBM, you can see behind the iris, where you might see something like plateau iris."

• ***Assess the IOP, nerve and visual fields***. Surgeons say that, though patients with higher pressures preop tended to get more pressure lowering in studies, it doesn't mean all severe glaucoma patients should just get cataract surgery. "I think, in general, it's better to be doing cataract surgery alone on mild to moderate glaucoma patients and those without a very high pressure," says Atlanta glaucoma and cataract surgeon Reay Brown. "So it would be better to operate on someone who doesn't have split fixation visual fields or pressures that are already far too high. It's best to select patients who are maybe controlled on a couple of medications, or have pressures that are maybe a little higher than you'd like on medical therapy and do the cataract surgery alone on them. Then, afterward, you can regroup and see whether a further glaucoma operation is even needed."

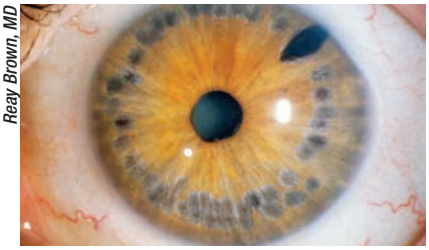
In addition to IOP, the other two keys to assessing the severity of a patient's glaucomatous damage are visual fields and the state of the optic nerve. Dr. Noecker says a mix of imaging and microscopic examination can tell most of the story. "The optic nerve is the biggest factor," he says. "The more damaged the nerve is, the more likely we'll do a combined procedure, because we don't want that optic nerve to get any worse. If they have a great-looking

optic nerve and a pressure problem, cataract surgery alone is an attractive alternative. It's the ones with these precarious optic nerves—really thinned out, big cups, thinning of the rim, maybe peripapillary atrophy, a disc hemorrhage on the nerve or a retinal nerve fiber layer defect—those are all high-risk characteristics. We'll certainly think about doing something more in those patients, since they're more diseased." OCT of the optic nerve can also be useful, says Dr. Noecker. "Here, again, you're looking for thinning of the nerve fiber layer. The important locations are superior and inferior, with the most important, most localized areas being inferotemporal and supero-temporal. The OCT correlates with our nerve exam and visual fields, and will help guide us. The more red we see on the test, the more we worry about it."

With visual fields, also, the worse they are, the less-inclined surgeons are to rely on cataract surgery alone. "Anyone with a visual field defect getting close to fixation which will impair his vision or who has a central island will need a combined procedure," says Dr. Noecker. "If he's at high risk we don't want his defect to get worse and move into the middle of his vision. I think severe disease with visual field loss above and below the horizontal meridian is a high-risk characteristic, as well."

Dr. Asrani feels similarly, saying, "I consider a combined procedure if the patient has a paracentral visual field defect, especially in the inferior paracentral area. If that's the case, a postoperative pressure spike—which is a risk that's quite high in any cataract procedure—might cause him to have significant worsening of the visual field damage. In those cases, if I'm unable to use oral Diamox in the postop period, such as for the first couple of days, I'll consider a combined surgery.

"The other scenario where I'd consider a combined procedure," Dr. Asrani continues, "is if the person is allergic to a variety of medications and the optic nerve has already been compromised to a fair extent. In that case, it makes sense to do a combined procedure for the sake of convenience. Since we're going to remove the cataract anyway, we might as well do a combined surgery at that time. Here the decision is being driven by the fact that the patient is allergic to a lot of medications, so you don't have a lot of options to treat the worsening glaucoma. Of course, this would be in the setting of moderate to severe glaucoma, but not mild. If the patient had mild glaucoma and it was controlled before the glaucoma surgery, there's a good chance he or she will be controlled after surgery, too."



Reay Brown, MD

Surgeons say a patient with angle closure can often benefit from cataract surgery in terms of a lower IOP postop.

Beneficial Maneuvers

There is a small gray area between cataract surgery alone and combined procedures in which some surgeons say you can boost your odds of getting a good result from cataract surgery. This area consists of performing a procedure preop, or a surgical maneuver during the actual cataract surgery.

"I always try to perform SLT prior to cataract surgery," says Dr. Tsai. "I believe—and this is extrapolation from our ALT experience—you have a better effect from laser trabeculoplasty if it's performed prior to cataract surgery than after. So, if I'm contemplating cataract surgery in a patient with glaucoma, the first thing I'll look at is if he's had SLT or ALT. If he hasn't, and he has an open angle and a diagnosis that will respond favorably to SLT, then I'll suggest we do it prior to the cataract surgery."

Dr. Brown says that an additional maneuver during the cataract surgery can help increase the odds of decreasing the pressure in certain patients. "If the angle is closed with PAS, then that might be a case where you perform goniosynechialysis during the cataract surgery," Dr. Brown avers. "You grasp the iris with forceps and pull it out of the angle, removing the iris from the surface of the trabecular meshwork. The idea is to give the aqueous access to the meshwork."

The Specter of the Spike

Even though a glaucoma patient may appear to be well-suited to have an IOP decrease with cataract surgery alone, surgeons say you have to be wary of postop IOP spikes.

"The postop IOP spike is one of the concerns of doing cataract surgery alone," says Dr. Tsai. "As a surgeon, you assume that the trabecular meshwork isn't functioning normally since the patient already has glaucoma. They're more at risk for a pressure spike. To decrease the risk, you will have to pay close attention to not overfilling the eye with viscoelastic during the cataract surgery, and to make sure to remove all the viscoelastic at the end of surgery. We're getting better with modern cataract surgery, however, since we currently use less viscoelastic and remove it more completely afterward.

"One thing to consider is that a substantial number of glaucoma patients have exfoliative syndrome that's either diagnosed or undiagnosed," he continues. "Exfoliative syndrome tends to pose a higher risk of vitreous loss and/or zonular dehiscence/instability,

and the glaucoma tends to be more aggressive. If you have a patient with exfoliative glaucoma, you have to be confident that you'll be able to control his or her IOP postoperatively, and this is one of the reasons why we used to perform a lot more combined procedures some years ago. Now, with smaller incision surgery, the tendency for glaucoma surgeons is to perform cataract surgery alone, which does lower IOP by itself, in patients with mild to moderate glaucoma, thereby not subjecting them to the risks and the longer postoperative recovery period of a combined procedure."

Glaucoma medication at the time of surgery can be crucial to blunting a spike. "My partner gives everyone Diamox at the time of cataract surgery," says Dr. Brown. "I give timolol at the end of surgery, though many of the glaucoma patients are already taking it. I also make sure that the patients use their glaucoma drops the day of surgery so they don't miss a round or two of doses, which I think is very important. You don't want to get off on the wrong foot, because if you look back at the patients who do poorly, you'll see that the patients with the pressure spike on the first day after surgery are at much higher risk for having problems with prolonged pressure elevation."

Dr. Brown says that, if you select the patients correctly and they achieve a postop IOP benefit after cataract surgery, it's a great feeling because it was relatively easily acquired compared to other surgeries or interventions. "That's the best thing about it: There's not much drama involved with it," he says. "There's enough drama in glaucoma treatment already." REVIEW

1. Poley BJ, Lindstrom RL, Samuelson TW, et al. Intraocular pressure reduction after phacoemulsification with intraocular lens implantation in glaucomatous and nonglaucomatous eyes: Evaluation of a causal relationship between the natural lens and open-angle glaucoma. J Cataract Refract Surg 2009;35:11:1946.
2. Yudhasompop N, Wangsupadilok N. Effects of phacoemulsification and intraocular lens implantation on intraocular pressure in primary angle closure glaucoma (PACG) patients. J Med Assoc Thai 2012;95:4:557-60.

Surgeons Grapple With the Femtosecond

Walter Bethke, Managing Editor

Cataract surgeons discuss the femtosecond laser and their approach to all aspects of cataract surgery.

Probably not since the first wave of femtosecond lasers designed for use in LASIK has there been so much discussion of the potential and drawbacks of a technology as there has been with femtosecond cataract surgery. In this month's e-survey on cataract technique, surgeons get to voice their opinions on the technology, from votes of support for it as the wave of the future, to questions about its clinical outcomes and financial viability. Also, surgeons take time out from the femtosecond fray to weigh in on other cataract topics, such as their favorite techniques, maneuvers and anesthesia methods.

These are just some of the findings from this month's e-survey on cataract surgery. The e-mail survey was opened by 1,275 of 10,000 subscribers to Review's electronic mail service (13 percent open rate), and of those, 173 (14 percent) responded. To see how your techniques compare with theirs, read on.

Femtosecond-assisted Surgery

On the survey, 8 percent of the surgeons currently perform femtosecond-assisted cataract surgery. R. Wayne Bowman, MD, from Dallas says he appreciates the laser's "consistency and accuracy," and a surgeon from Minnesota feels similarly, saying he likes its "improved reproducibility," but cites "cost and learning curve" as less desirable aspects. "I love it," says Norfolk, Va., surgeon John Sheppard. "However, removing sub-incisional cortex is more difficult, and it is costly and more time-consuming. There are safety advantages due to better wound healing, less phaco time and a stronger capsulorhexis edge, and it's great for promoting and growing the practice." Los Angeles surgeon James Salz also accepts the good with the bad with his femtosecond laser. "I love the rhexis, arcuate incisions and chopping," he says. "I do not like it for primary and side-port incisions as I prefer to place them exactly where I want them [more limbal] and the femto incisions are usually off my preferred location, as it makes the incisions more corneal."

Looking ahead, 70 percent of surgeons say they're unlikely to perform femto-assisted surgery in the current year. However, 21 percent think they're somewhat likely to do so, and 9 percent say they're very likely to perform it. At this point, uncertainty reigns, as many surgeons find it hard to justify pulling the trigger on the technology. "The femto-

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INDICATIONS AND USAGE:
TRAVATAN Z® Solution is a prostaglandin analog indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration:
One drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions:
Pigmentation: Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation likely to be permanent.

Eyelash Changes: Gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible.

Adverse Reactions:
Most common adverse reaction (30% to 50%) is conjunctival hyperemia.

Use In Specific Populations:
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information please refer to the accompanying brief summary of prescribing information on adjacent page.

Reference:
1. Dubiner HB, Noecker R. Sustained intraocular pressure reduction throughout the day with travoprost ophthalmic solution 0.004%. *Clin Ophthalmol.* 2012;6:525-531.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
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.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

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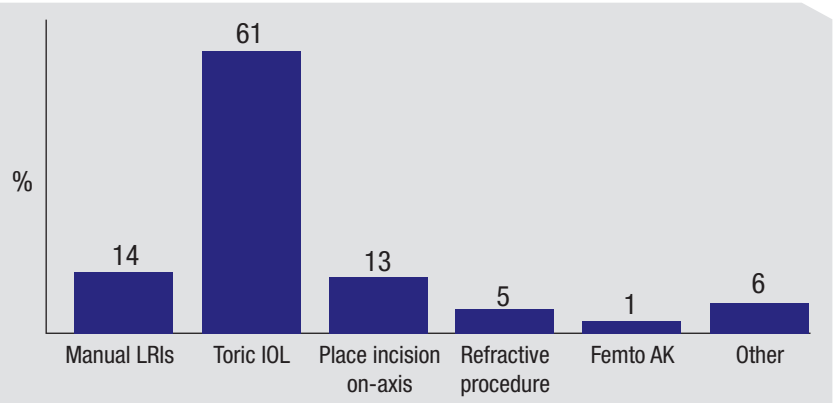
second laser and phacoemulsification machine are separate technologies utilized in separate theaters," says a surgeon from Texas. "I feel this is inefficient surgery, and anticipate the technology will someday merge into a single unit or platform with aspiration handpieces optimized to remove a pre-segmented nucleus. Also, the current standard monofocal intraocular lens results are good enough as to not justify the capital investment or recurring click fee for the femtosecond laser." A surgeon who wished to remain anonymous says the financial hurdle is still the major sticking point. "The laser still costs too much," he says. "Despite being in a surgery center with 15 operating physicians, we cannot make the numbers work at this time. Until insurers start to cover the cost—at least partially—or until manufacturers drop the price, femto cataract surgery is going to be a boutique item." Luther Fry, MD, of Garden City, Kan., says, "There's no benefit, it's expensive and more than doubles my surgical time." Ben Mackey, MD, of Corbin, Ky., says he's unlikely to do it. "My surgery center cannot justify the expense," he says. "And I cannot justify the expense and anticipated slow down." David Brigham, MD, of Des Peres, Mo., adds that lens technology may hurt some of the need for the femtosecond. "The prospect of the toric multifocal IOL coming soon to the United States will make astigmatic keratotomy less necessary in premium cases," he says. "There will be less incentive to use the femto in other types of IOL implantation as it will increase the time and the cost of each case. I really think most patients are cost-conscious and are reluctant to spend out of pocket, especially those over 80. Younger people in their 60s and 70s are easier to convince about the benefits of premium lenses, and it follows that they would be the best candidates for the femto laser—but the $750 extra will take a little more salesmanship."

There are also cataract surgeons who don't use the femtosecond laser at the moment, but see the device as the future of cataract surgery and would rather be on the train than under it. One surgeon from Tennessee says he's likely to use it due to the "demands of the market." A surgeon from Ohio is eager to do it, even saying, "I might change jobs to a location where it's available." A surgeon from Tennessee doesn't want to get left behind. "You have to keep up with the Joneses!" he says. "I believe the future of cataract surgery will involve some version of these lasers, and we need to keep up with the technology."

Preferred Way to Manage Astigmatism in Cataract Patients

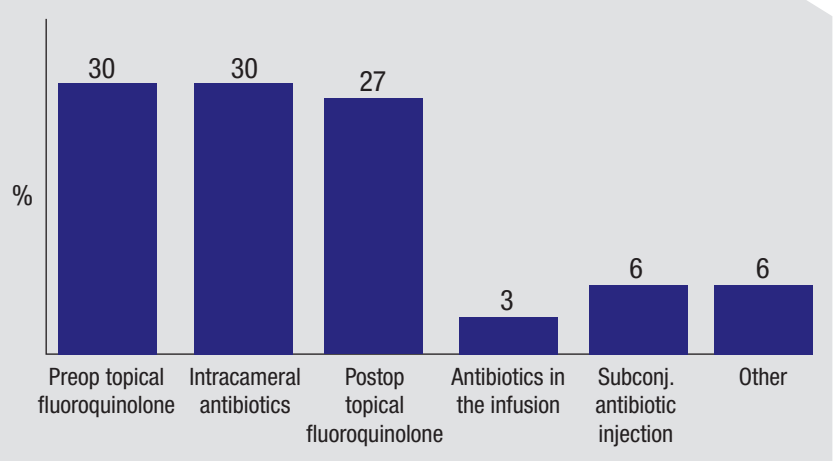


Fighting Infection

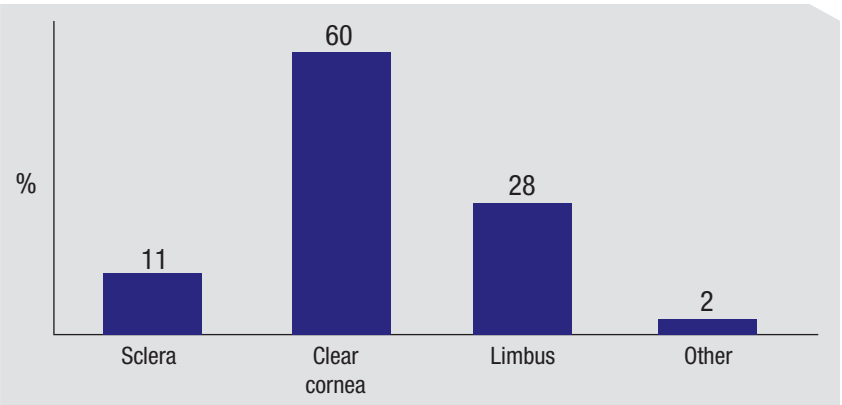
When it comes to the best infection prophylaxis method, in addition to the use of povidone iodine, 30 percent think preop topical fluoroquinolones are best, 30 percent prefer an intracameral antibiotic injection and 27 percent like postop topical fluoroquinolones. Less popular are subconjunctival antibiotic injection (6 percent) and the use of antibiotics in the infusion (3 percent). Another 6 percent choose some other type of prophylaxis. Some surgeons chose more than one option.

"I use topical fluoroquinolones," offers Mark Volpicelli, MD, of Mountain View, Calif. "And I also use

Best Infection Prophylaxis (Besides Povidone Iodine)



Preferred Cataract Surgery Incision Site



an intraoperative injection of vancomycin at the end of the procedure." Another surgeon says he thinks "an immediate postop Betadine drop" is best. Lan Pham, MD, of Yorktown Heights, N.Y., combines approaches, saying, "I prefer pre- and postop topical antibiotics, as well as great, well-sealed corneal incisions."

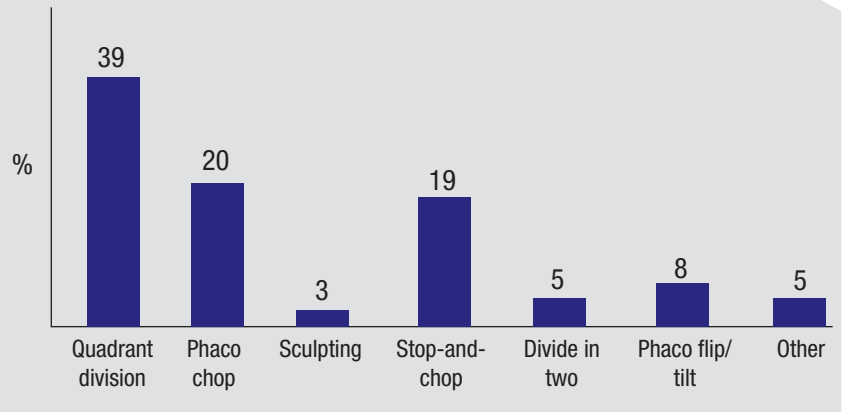
Controlling Astigmatism

Most of the surgeons, 61 percent, prefer to manage a patient's astigmatism with a toric IOL. Fourteen percent like manual limbal relaxing incisions, 13 percent prefer placing the clear corneal entry wound on the axis of astigmatism, 5 percent think a postop refractive procedure is best and 1 percent perform femtosecond astigmatic keratotomy. Six percent choose some other method, including postop spectacles.

"There is good predictability of astigmatism control with a toric IOL," says Nick Mamalis, MD, of Salt Lake City. "This method avoids any need for corneal incisions or laser treatment of the cornea." Dallas' Dr. Bowman thinks a toric lens avoids some problems that plague other methods. "It has less regression, less dry eye and less weakening of the eye," he says. "It's also more consistent and stable." Sid Moore, MD, of Macon, Ga., likes toric lenses, but sees value in the other approaches. "The toric lens has greater predictability than an LRI," he says. "I do employ an on-axis incision whenever possible, and perform manual limbal relaxing incisions when toric IOLs are not an option, such as in the case of multifocal IOLs." Toric IOLs are "predictability at its best," avers a surgeon from California. A surgeon from Maine likes toric lenses, but says his local market forces him to be brutally realistic. "When anything is done at all for astigmatism, I use a toric IOL," he says. "However, in the overwhelming majority of patients, even those with significant cylinder of 2 D or more, they are not willing to pay even $300 extra plus the cost of the implant. So, these lenses are rarely used."

In the LRI camp, Michael Sala, DO, of Erie, Pa., says, "They've given me good results for years," and a surgeon from Washington agrees, saying, "They're less reliable, but they're cheap and easy to do." Donna Qahwash, DO, of Wyandotte, Mich., says she prefers doing LRIs to other methods because "They represent less cost to the patient."

Preferred Nuclear Fragmentation Technique



Cataract Techniques

Surgeons also discussed various other aspects of cataract surgery, from nuclear fragmentation to bimanual surgery.

• ***Fracturing the nucleus.*** When surgeons attack the nucleus, 39 percent prefer to do it with quadrant division; 20 percent like phaco chop; 19 percent prefer a stop-and-chop maneuver; 8 percent like phaco flip/tilt; 5 percent divide the nucleus into two halves first; and 3 percent like sculpting maneuvers. Five percent say they like some other approach.

"With quadrant division, most of the phaco energy is exerted posterior to the level of the iris and a greater distance from the corneal endothelium," says a surgeon from Delaware on why he prefers the

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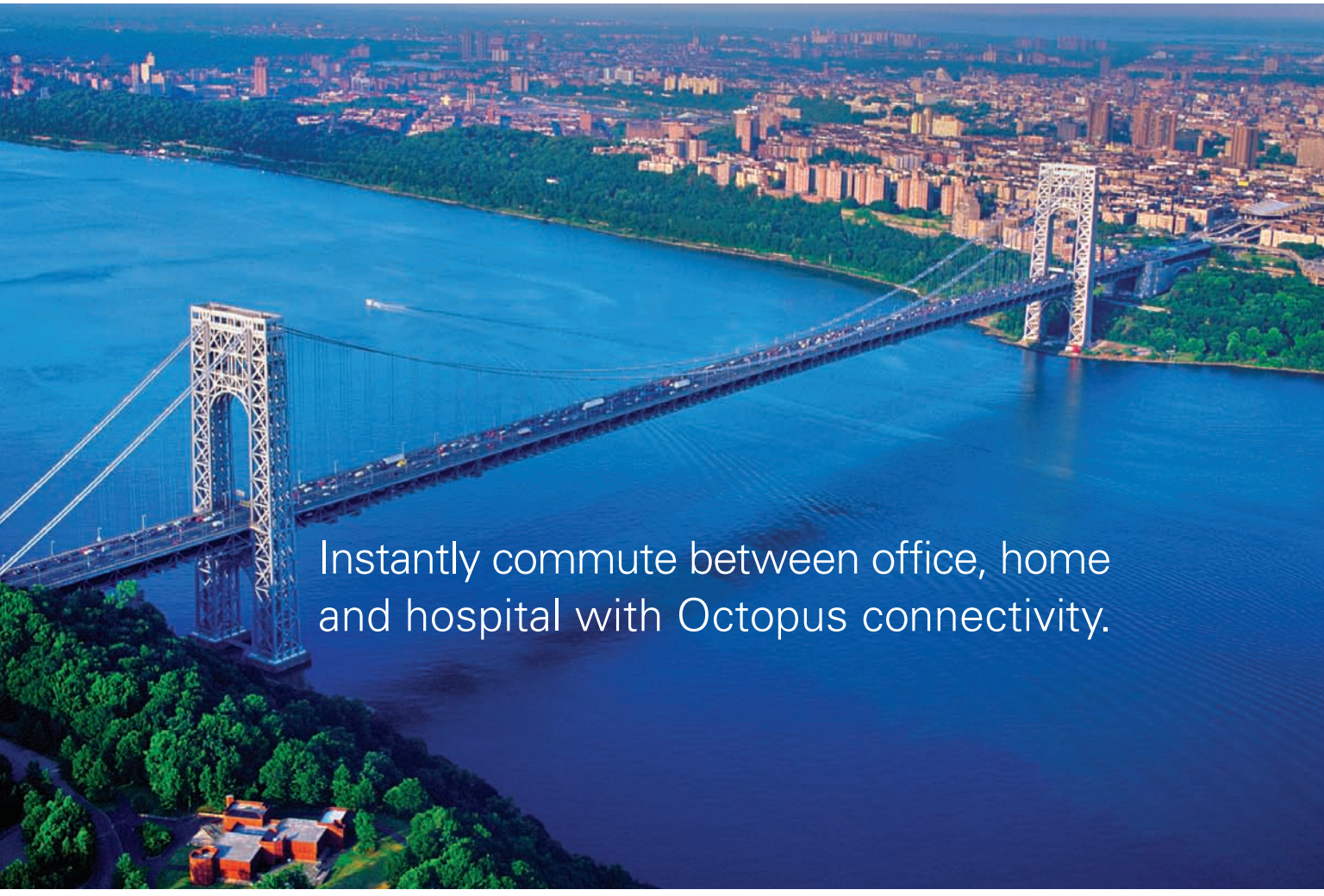

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method. A surgeon from Louisiana also likes quadrant division. "It's easy to manage," he says. "I was not taught phaco chop and feel more comfortable with quadrant division, and have very few complications." A surgeon from California concurs, saying, "For me, quadrant division is safest in that it exerts less zonular traction and is the most efficient, time-wise."

However, the proponents of phaco chop say that in the right hands, it has a good safety profile, too. "Phaco with a vertical chopping technique minimizes ultrasound time and poses less risk to the capsule," says Bruce Hodges, MD, of Frederick, Md. Kentucky's Dr. Mackey says, "Phaco chop is usually more efficient than other techniques. It's less dependent on pupil size, also." Dr. Moore agrees, saying the features he appreciates most about chopping are "Efficiency, adaptability, safety and decreased energy."

The stop-and-chop proponents think it's preferable to the other approaches, however. "It's easy, consistent and quick," says a surgeon from California. Dr. Mamalis says that with stop-and-chop he gets "good control of the nucleus during phaco with an initial groove." A surgeon from California agrees, saying, "The central groove clears out some space centrally so that it's easier to chop the remaining half and bring the piece into the middle for removal." Patrick Chin, MD, of Westwood, N.J., says that stop-and-chop "allows me to disassemble the nucleus easily and consistently for all types of nuclear densities and minimize the use of phaco energy."

• ***Incision location.*** Sixty percent of surgeons use clear corneal wounds, 28 percent prefer limbal, 11 percent use the sclera and 2 percent use some hybrid of those. The average incision size cited was 2.56 mm.

Dr. Salz says he prefers using the limbal region. "The wound is near-clear, with a vertical groove of 3 mm and an entry incision of 2.75 mm," he says. "I like to make the groove in the limbal arcade so it bleeds slightly, as I think you get faster healing at that location."

• ***Bimanual and C-MICS.*** A bimanual technique in which the infusion and aspiration are done through separate handpieces has only caught on with 20 percent of surgeons. Respondents offer a variety of reasons why it hasn't worked for them. "I don't find that chamber stability is as good as micro-coaxial and since my wound will have to be enlarged, there is no benefit," says New Jer-

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sey's Dr. Chin. However, Louise Davis, MD, of Beverly Hills, Calif., prefers bimanual, saying, "It's the safest for the capsule."

Another alternative technique embraced by some surgeons (35 percent on the survey) is coaxial micro-incision surgery, or C-MICS. "It makes for safer removal of the lens," says a surgeon from Louisiana. "It also provides good anterior chamber stabilization." However, some surgeons point out that such small-incision techniques don't keep the incision small throughout the entire case. "There's no distinct advantage at this time in terms of safety or efficacy since the incision size is expanded to allow IOL insertion," says a surgeon from California.

• ***Best practices.*** Surgeons also shared the tips and techniques they've developed to make procedures run more smoothly and be more successful. "The continuous curvilinear capsulorhexis is the most important part of the cataract surgery," says Dr. Mamalis. "Take the time to perform a well-centered, properly sized CCC and the remainder of the case will proceed more smoothly." Dr. Sheppard has several tips, and says a relatively mundane surgical maneuver can actually prove to be very useful. "An unheralded way to prevent post-cataract endophthalmitis is a very thorough I/A of the viscoelastic at the conclusion of the case: It dilutes organisms to manageable titers," he says. "Also, use dispersive viscoelastic on the endothelium before phaco to preserve corneal thickness, know that every patient is a candidate for a premium IOL until proven otherwise and treat every patient as if he or she were your dad or mom." Sandy Yeh, MD, of Springfield, Ill., has a neat tip for streamlining the surgery day: "We include dilating drops in the patients' surgical kits for them to use to self-dilate the morning of the surgery," she says. "They arrive at the ASC fully dilated and ready to go. This saves a great deal of nursing time, and if one patient isn't ready the next will be ready to go. Also, in order to create a 5-mm capsulorhexis for a premium lens, mark the cornea with a 6-mm PRK marker and then target the capsulorhexis inside of this."

In the end, surgeons say an experienced mind is the most valuable piece of technology. "Think," advises Warren Cross, MD, of Houston. "If anything seems even slightly strange, stop, look and think for a minute—because after 50,000 cases something probably is different or wrong, even if it's not obvious. Trust your instincts." REVIEW

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Keys to Managing Weak Zonules

Michelle Stephenson, Contributing Editor

The best approach may include a combination of adjunctive devices.

Zonular weakness can be caused by disease or trauma, and its presence can make cataract surgery more challenging. Fortunately, there are adjunctive devices to effectively manage it and achieve successful outcomes.

Causes

Certain diseases of the eye are associated with zonular weakness or insufficiency. The most common one is pseudoexfoliation. "In patients with pseudoexfoliation, when you look at the eye, it looks like part of the lens capsule is peeling. We have realized that these are actually deposits of material on the lens capsule, but it looks like a layer flaking off the lens capsule, hence the name," says Uday Devgan, MD, a surgeon from Los Angeles.

All images: Uday Devgan, MD

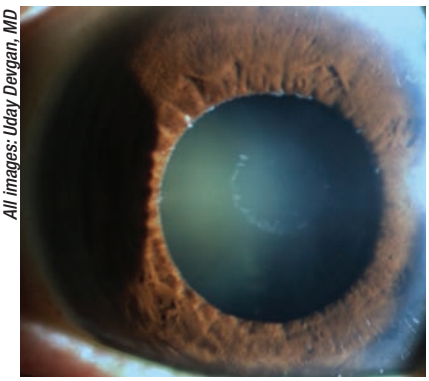

Figure 1. This patient has significant pseudoexfoliation material on the anterior lens capsule and iris margin as well as shallowing of the anterior chamber and limitation of pupillary dilation. We can expect surgical challenges related to loose zonules during this surgery.

Pseudoexfoliation can almost always be seen preoperatively. It can make the zonules very weak and can also affect pupil dilation.

There are varying degrees of pseudoexfoliation. Some cases are very mild with a few subtle signs, and cataract surgery can be uneventful. Then, in some cases of severe pseudoexfoliation, when the surgeon attempts to remove the cataract, the zonules can fail and the whole cataract can fall into the back of the vitreous.

"To determine the severity of pseudoexfoliation preoperatively, assess how well the pupil dilates, and compare the anterior chamber depth to the axial length of the eye," Dr. Devgan says. "In the normal eye, the zonules hold the lens (the cataract) in place. If the zonules are weak, that cataract tends to push forward and push the back of the iris toward the front of the eye. As it pushes, it shallows the anterior chamber, so the warning sign is presence of a shallow anterior chamber in an eye where

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INDICATIONS AND USAGE: DUREZOL® Emulsion is a topical corticosteroid that is indicated for the treatment of endogenous anterior uveitis.

Dosage and Administration

For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

Contraindications: DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions

- Intraocular pressure (IOP) increase – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Cataracts – Use of corticosteroids may result in posterior subcapsular cataract formation.
- Delayed healing – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses.

Adverse Reactions

In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion please refer to the brief summary of prescribing information on adjacent page.

Reference: 1. DUREZOL® Emulsion Package Insert.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.
Endogenous Anterior Uveitis
DUREZOL® Emulsion is also indicated for the treatment of endogenous anterior uveitis.

DOSAGE AND ADMINISTRATION
Ocular Surgery
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

Endogenous Anterior Uveitis
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

DOSAGE FORMS AND STRENGTHS
DUREZOL® Emulsion contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

WARNINGS AND PRECAUTIONS
IOP Increase
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections
Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections
Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects; posterior subcapsular cataract formation; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® Emulsion is administered to a nursing woman.

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.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Difluprednate was not genotoxic *in vitro* in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Risk of Secondary Infection
If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

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U.S. Patent 6,114,319

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you wouldn't expect it. Usually, shallow anterior chambers are associated with short, tiny eyes. When you have a normal-sized eye, but the anterior chamber is shallow, that may be a sign."

Some patients with pseudoexfoliation have frank phacodonesis. "If we see that preoperatively, it is a big issue. Then, in very severe cases, the zonules are so compromised already that we see a gap where the zonules are absent or missing or the cataract itself is decentered," he adds.

In the OR, at the beginning of the case, one of the first signs of weak or insufficient zonules is a lens capsule that is not taut. "Normally, the lens capsule is taut like the head of a drum. If a drum is taut, it can be easily penetrated with a sharp instrument," Dr. Devgan says.

According to David Chang, MD, who is in practice in Los Altos, Calif., zonular laxity is often present with ultrabrunescent cataracts. "Of course, the zonules are concealed from our slit-lamp view by the peripheral iris and so it generally is not until the capsulorhexis step is performed that the surgeon can gauge the degree of zonular laxity," he explains. "Signs of abnormal zonular integrity include difficulty perforating the central capsule with the cystotome, excessive wrinkling and mobility of the anterior capsule, and excessive movement of the peripheral lens capsule as the flap is maneuvered with capsule forceps. All of these signs indicate that the anterior capsule is not taut and is not sufficiently stretched and anchored by centrifugal zonular traction."

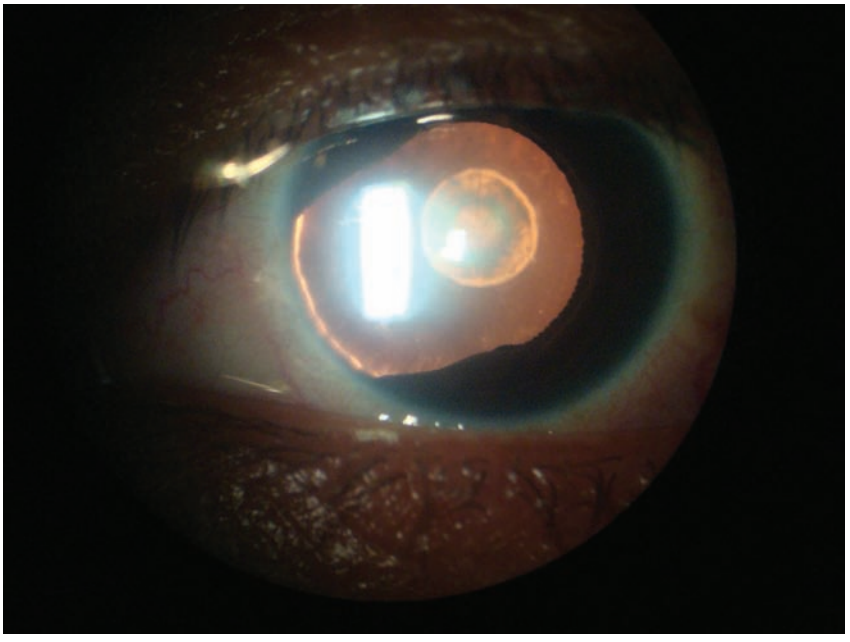

Figure 2. This patient has a congenital absence of zonules and iris in one sector as well as a posterior polar cataract. Care must be taken to provide additional capsular support during surgery and to ensure long-term stability of the intraocular lens.

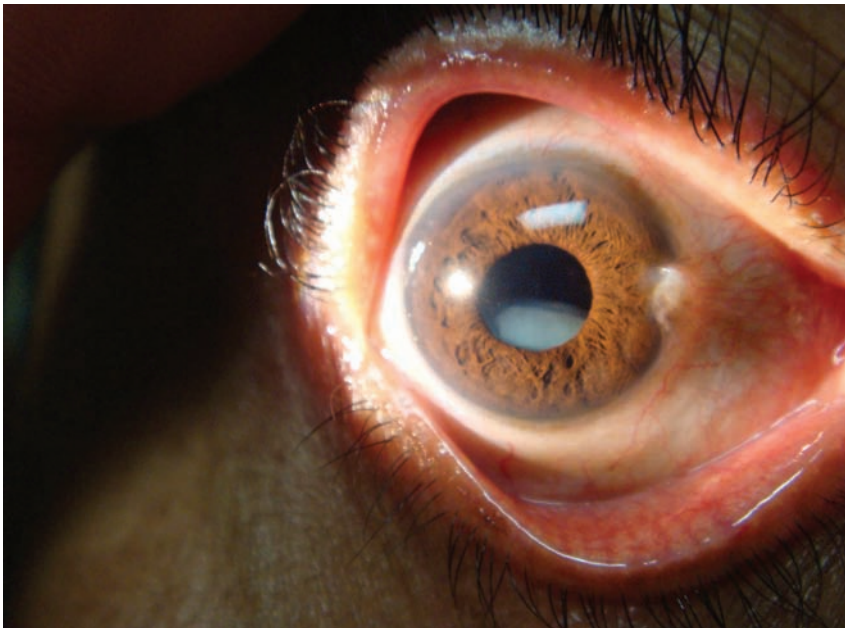

Figure 3. After sustaining trauma, many of the zonules ripped, causing the cataract to become dislocated into the vitreous cavity. In this case, a pars plana approach by a vitreoretinal surgeon will likely be the best option for cataract removal. A second surgery to place a suture-fixated IOL or an anterior chamber IOL can be done later.

Management

Once it has been determined that a patient has zonular weakness, the surgeon must decide whether to proceed with surgery while being extra cautious, or whether to use adjunctive devices to help support the capsule. According to Richard Hoffman, MD, who is in practice in Eugene, Ore., there are basically two devices to choose from: a capsular tension ring or capsule support hooks.

Dr. Hoffman notes that he used to prefer capsular tension rings, but

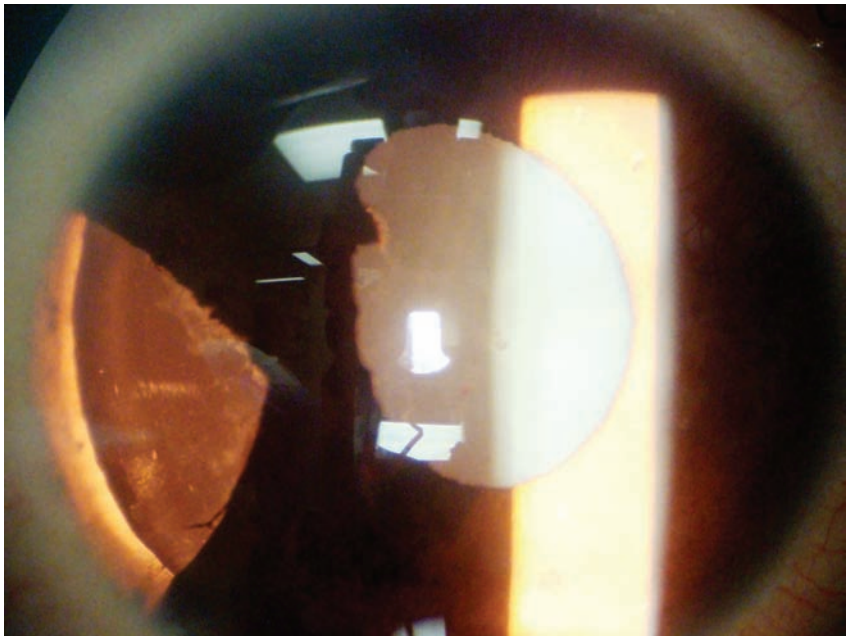

Figure 4. After being hit in the eye with a baseball, this patient suffered traumatic iris damage and zonular loss. While her condition can be addressed conservatively now, once a cataract develops, there will be surgical challenges related to poor zonular support.

is now moving more toward using the hooks. "You can also use a combination of both," he says. "You can put the capsular tension ring in before you start the phacoemulsification and then support the capsule with capsule hooks in extreme cases. Even in eyes that have had significant phacodonesis, lately I have just been using capsule hooks."

Capsular tension rings support the zonules centrifugally but they don't necessarily support the up and down movement of the lens. "I actually started using capsule hooks in patients who had zonular weakness and had previous vitrectomies because there is no vitreous support behind the lens and you get a lot of anterior and posterior movement of the capsule either during the chopping maneuvers or during the phaco. This seemed to support the zonules better than just a capsular tension ring," says Dr. Hoffman.

Additionally, Dr. Hoffman notes that it can be difficult to remove the cortex if a capsular tension ring is used at the beginning of the procedure. For this reason, many surgeons tend to place the ring at the end of the procedure or near the end. "However, if you use a capsular tension ring, it is going to be most valuable at the beginning of the procedure, but it makes removal of the cortex a little more challenging," he adds.

Dr. Chang agrees. For severe zonular laxity, he uses capsule retractors to stabilize the capsular bag. "One can use flexible iris retractors for this purpose, but capsule retractors have a much longer tip that better supports the periphery of the capsular bag. The retractors provide numerous advantages for phaco. They support the bag in the axial direction, they provide rotational stability so that the nucleus can be rotated without stripping the weakened zonules, and they restrain the capsular equator from being aspirated into the phaco tip. Finally, compared to a capsular tension ring, capsule retractors do not impede aspiration of the cortex," he says.

He typically delays implantation of a capsular tension ring until after the cortex is evacuated, but prior to removal of the capsular retractors. "In this way, the bag is supported and stabilized against the decentering forces of the capsular tension ring as it opens," he explains.

Another option is an Ahmed ring segment, which is a smaller segment of a capsular tension ring, Dr. Hoffman says. "Especially if a patient has a subluxed lens, I will put in an Ahmed ring segment. You can support a ring segment with a hook to support that quadrant of the lens. I will usually use the capsule hooks, then if I need to sew in a segment, I will do that after I've removed the cataract," he explains.

His current approach in a patient with a fairly hard cataract and pseudoexfoliation starts with staining the capsule and performing the capsulorhexis. Usually, the capsulorhexis will confirm that there is some zonular weakness. Then, he places three equally spaced capsule hooks and performs the phacoemulsification. Following phacoemulsification, he places a capsular tension ring.

"The reason I put a capsular tension ring in at the end of the procedure is twofold. First, I think it decreases the severity of anterior capsule phimosis. It may help support the zonules so that patients are less likely to have late lens subluxations but it does not guarantee the avoidance of that. Patients still get subluxations of their capsular bag and their lens with the capsular tension ring in place, but it's possible that it might delay the onset of that. The main reason is that there are a small percentage of patients with pseudoexfoliation who undergo cataract surgery, and there is not much zonular weakness immediately after surgery. Then, seven to 10 years after their surgery, the zonules come loose, and

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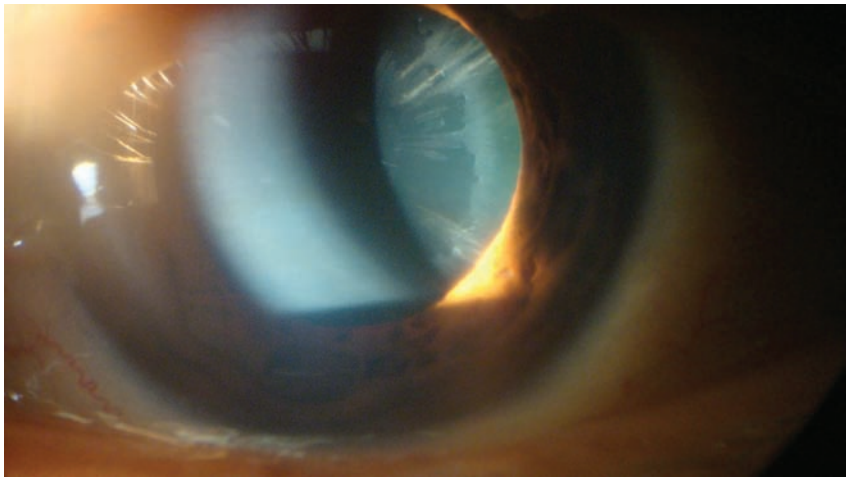

Figure 5. While this patient has extensive pseudoexfoliation material on the anterior lens capsule, the pupil dilation is quite good, the anterior chamber is deep and the zonular support is adequate for an uneventful cataract surgery.

their lens subluxes. If there is a capsular tension ring in the capsular bag, it makes it very easy to sew the bag to the sclera. You don't have to worry about where the haptics are. That's my reason now for putting capsular tension rings in my pseudoexfoliation patients, usually at the end of the procedure," he explains.

Only patients with pseudoexfoliation experience late subluxations. "With trauma patients, pretty much what they have the week after surgery is what they are going to have for the rest of their life. It is unlikely that they will get progressive zonular degradation and late lens subluxations," Dr. Hoffman adds.

Dr. Devgan says that he prefers the Mackool Capsule Support hooks, made by multiple manufacturers. Capsule support hooks go through the side-port incisions to hold and stabilize the capsule. "Once the cataract is removed, if there is a focal area of zonular weakness, and you don't anticipate it getting worse in the future, you can put in a capsular tension ring. The ring distributes the forces more evenly and helps stabilize the capsule. In some situations where there is a more significant amount of weakness, you may have to put in a capsular tension ring that has a little eyelet in it, such as a Cionni ring. The eyelet allows you to tie a suture through it and to fixate the lens and the whole capsular bag to the sclera," he explains.

He notes that the capsular bag is not salvageable in some patients and must be removed before the procedure. "Then, you will have to sew a lens in either to the back of the iris or trans-sclerally or maybe put an anterior chamber lens inside the eye. The key is to not be surprised and to try to identify things ahead of time. Be very alert when you first start the capsulorhexis, and look for weakness. If it's there, prepare for it," he says.

If the zonules are weak due to trauma, the patient will most likely have a good outcome because he or she is unlikely to suffer additional trauma in the future. "In contrast, pseudoexfoliation is a progressive disease over time, and I've only seen the ball roll downhill. However, you can make it roll downhill a little slower," Dr. Devgan adds.

Because patients with severe pseudoexfoliation can get late dislocation of the entire lens, Dr. Devgan places a capsular tension ring or uses a three-piece lens design, because they are more amenable to suture fixation. "If a patient's lens starts to decenter five years after surgery, I can go back in the eye and suture that lens in place to the back of the iris or the sclera," he adds.

Other Tips

Dr. Hoffman notes that if he has a pseudoexfoliation patient whose capsule does not wrinkle significantly during the capsulorhexis, then he proceeds with surgery without any adjunctive devices. He recommends bringing the nuclear fragments up into the anterior chamber to phaco them, because that puts less stress on the zonules. Additionally, avoiding excessive downward pressure on the lens during decompression following hydrodissection, and doing horizontal chopping rather than vertical chopping or sculpting puts less stress on the zonules. "You can get through many of these cases without using the devices if the zonules are in decent shape and you are very careful and gentle with your maneuvers inside the eye," he says.

Dr. Devgan notes that one trick for performing a capsulorhexis in a patient with weak zonules is to hold the capsule with one forceps with your left hand as you tear it with your right hand. "Then, it will be easier to complete the capsulorhexis. Alternatively, you could use a femtosecond laser as long as the pupil dilation is good," he says.

According to Dr. Chang, in a patient with weak zonules, phaco chop provides particular advantages because the nucleus is immobilized by the phaco tip against the centripetal force of the chopper. Compared to sculpting techniques, this reduction in stress on the zonules is very evident when chopping is visualized from the Miyake-Apple view in cadaver eyes. REVIEW

ALLERGIC CONJUNCTIVITIS:

A Growing Patient Problem

Many ophthalmologists talk about ocular surface disease and the frequent patients with dry eye and meibomian gland disease, but they often list allergic conjunctivitis as a far third—despite the fact that over the past several years, we're seeing more and more patients present with this condition. While clearly a growing patient problem, treatment of the symptoms of allergic conjunctivitis is also an opportunity.

In an attempt to put this condition on the radar where it deserves to be, four well-known clinicians participated in a webinar, during which they discussed the prevalence of allergic conjunctivitis; the phases and treatments of the condition; and the use of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% for itching associated with allergic conjunctivitis. The following pages briefly summarize highlights from the event.

ALLERGIC CONJUNCTIVITIS ORIGINS AND PREVALENCE

Paul M. Karpecki, OD

More than 20 percent of the general population suffers from allergic conjunctivitis.[1] Those who wear contact lenses might discontinue wearing their lenses; take a break from wearing them; cut back on their daily wear; or be switched to a new modality such as a daily disposables. Prompt and effective treatment of allergy symptoms will cut down on that hiatus time and possibly prevent patients from discontinuing wear.

Know the Enemy

Seasonal and perennial allergic conjunctivitis represent the two most common ocular allergies.[2] They are both type 1 (immediate) hypersensitivity reactions commonly grouped together under "allergic conjunctivitis" but the main differentiator is timing of symptoms.[3]

Commonly in seasonal allergic conjunctivitis, a significant peak in ocular symptoms occurs between April and June, and a second peak shows up between August and September, though this can certainly vary depending on where you live. Nonetheless, it's important to be aware of these key times. Perennial allergic conjunctivitis exists all year long because it's related to household allergens such as animal dander, dust mites and mold that are always present.[3]

Regional variations in seasonal allergic conjunctivitis are driven by climate and differences in pollen producers. In the west and desert regions, some plant allergens are present the entire year and when you get into the southern region, you'll see grasses all the way from January through to mid November/early December.

Identify and Destroy

Many times when patients visit the Ocular Surface Disease Clinic, we focus on dry eye, blepharitis and meibomian gland dysfunction. Patients with blepharitis may talk about itching that is more on their lids and patients with allergic conjunctivitis will complain about itching of the eye or canthal region, but they're certainly talking about symptoms of itching, so you have to differentiate. Both allergic conjunctivitis and MGD patients may complain of redness, grittiness and dryness, but allergic conjunctivitis patients tend to complain about itching first. Oftentimes, treatment with a combination agent such as an antihistamine-mast cell stabilizer will take care of the itch associated with allergic conjunctivitis.

Dr. Karpecki is Corneal Services & Ocular Disease Research Director at Koffler Vision Group in Lexington, Ky. He is also National Education Director, Optometric Medical Solutions.

THE PHASES AND TREATMENT OF ALLERGIC CONJUNCTIVITIS

Edward J. Holland, MD

As a type 1 hypersensitivity reaction, allergic conjunctivitis has three phases: ***Sensitization phase.*** IgE antibodies specific to the presenting allergen are created and bind to the surface of mast cells, making sensitization complete. The mast cells then begin to produce histamine. Prostaglandins and leukotrienes are also produced, and are the medians of inflammation; now the eye is primed for the signs and symptoms of allergic conjunctivitis.[4]

Early phase. If the eye encounters the same allergen that led to this sensitization, it will begin the early stage allergic reaction and during this process, the allergen binds to the IgE antibodies present on the mast cells. The mast cells degranulate in response to the allergen IgE complex and within minutes, histamine, prostaglandins, leukotrienes and the other chemotactic factors such as IL-5 are released, initiating the allergic response. These factors contribute to the patient experiencing itch.[4]

Late phase. Anywhere from two to six+ hours after the allergen exposure, the allergic reaction moves to this late phase and the chemotactic factors release from mast cell degranulation, attract and recruit and activate the other inflammatory cells, mediators and additional key cells. The presence of these additional immune cells and their byproducts will prolong and exacerbate the symptoms of allergic conjunctivitis.[4]

Treatment Review

A variety of approaches are available to us as clinicians to treat the itch associated with allergic conjunctivitis. The most fundamental approach is to avoid contact with allergens as much as possible. A variety of self-help remedies, including cool compresses, over-the-counter (OTC) artificial tears/lubricants, OTC topical antihistamines and vasoconstrictors are also at our disposal. Prescription options include non-steroidal anti-inflammatory drugs, topical corticosteroids, mast cell stabilizers, antihistamines as well as dual-action antihistamine-mast cell stabilizers such as BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%.

Our role is to assess symptom severity so we can provide the right treatment choice(s) and help our patients understand our recommendations, including how to use the OTC choices. We want to recommend a treatment that's quick, long lasting and gives complete relief for these patients.

Dr. Holland is Director of Cornea at the Cincinnati Eye Institute and Professor of Ophthalmology at the University of Cincinnati.

A BRIEF PRIMER ON BEPREVE

Stephen S. Lane, MD

Bausch + Lomb's prescription eye drop BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is approved in the United States for the treatment of itching associated with allergic conjunctivitis. It is a highly selective histamine H_1 receptor antagonist and a mast cell stabilizer. The BEPREVE® allergic conjunctivitis clinical trials were conducted in a Conjunctival Allergen Challenge, or CAC model, which is a consistent standard for evaluating the efficacy of allergic conjunctivitis treatments because it eliminates much of the variability associated with environmental studies.[5]

In this model, patients are evaluated for sensitivity to a specific allergen. Entry criteria into the study is a grade two or higher for itching and hyperemia individually.[5–8] With this response established, patients are given a dose of either the test agent or placebo. Following a specific interval—15 minutes to evaluate onset of action; eight hours or 16 hours to evaluate the duration of action—the patient is "challenged" with the allergen. In other words, the allergen is introduced into their eyes. They are then evaluated for signs and symptoms. A primary endpoint in the BEPREVE® studies was ocular itching, which was graded from 0 – 4 (a nine-point scale allowed 0.5 increments) that ranged from no itch to a very severe or incapacitating itch.[5–8]

Efficacy

The efficacy in the itch endpoint was compared to placebo at different time points. In terms of ocular itch and onset of action, 95 percent of eyes dosed with BEPREVE® achieved a clinically significant reduction in ocular itching at three, five and seven minutes post dose (n=156 eyes).[5–8] That's a reduction in itching score of at least one full unit, which is also statistically significant. When challenged eight hours post dose, 90 percent of the eyes treated with BEPREVE® had a clinically significant reduction in ocular itch, which is also statistically significant (n=156 eyes). (The eight-hour time period is considered the benchmark by the FDA for b.i.d. dosing.)

In patients with severe ocular itch of grade three or more, 68 percent of eyes treated with BEPREVE® had no ocular itching at three minutes post challenge in the onset of action visit (n=104 eyes).[5–8] Only three percent of eyes in the placebo group reported having complete elimination of itch at three minutes (n=98 eyes). These data suggest that a majority of patients, given a drop of BEPREVE® in the lane, can experience a substantial, if not complete, degree of relief from their itch before they even leave your office.

Dr. Lane is Medical Director, Associated Eye Care and Adjunct Clinical Professor, University of Minnesota.

A LOOK AT BEPREVE'S SAFETY TRIAL RESULTS

Richard L. Lindstrom, MD

As with efficacy, safety is also important. In addition to the two pivotal efficacy studies, BEPREVE® was evaluated in a six-week randomized placebo controlled multi-center safety study.[9,10] A total of 861 healthy subjects including pediatric patients as young as three years old were enrolled and dosed bilaterally for about 43 days. Safety evaluation included adverse events, vital signs, ophthalmological exams and ocular comfort.

This safety study also quantitatively assessed the ocular comfort of the drop. Again, the comfort of BEPREVE® was not statistically different from placebo at both 30 seconds and five minutes post instillation, with 92 percent of more than 6,400 ocular comfort scores reporting no discomfort.[9,10] The most common treatment-related adverse event reported in the six-week safety trial in normal volunteers was mild transient taste, in approximately 25 percent of subjects.[9,10] Other adverse events reported in at least two percent of subjects included eye irritation, headache and nasopharyngitis.

Of note, reports of dry eye were slightly higher (1.7%) in placebo-treated patients compared to BEPREVE®-treated patients (1.0%). Because many patients do have associated symptoms of dry eye and allergic conjunctivitis, this is an important clinical issue.[11]

Dr. Lindstrom is Founder and Attending Surgeon, Minnesota Eye Consultants and Adjunct Professor Emeritus, University of Minnesota Department of Ophthalmology.

INDICATION

BEPREVE® is a histamine H1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

IMPORTANT RISK INFORMATION

BEPREVE is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens–related irritation. Remove contact lenses prior to instillation of BEPREVE®.

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

Please see Full Prescribing Information for BEPREVE® on the Following Page.

References

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BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into the affected eye(s) twice a day (BID).(2)

--------DOSAGE FORMS AND STRENGTHS---------
Solution containing bepotastine besilate, 1.5%. (3)

----------------CONTRAINDICATIONS----------------
Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE® should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE®. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION
Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2. DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE® into the affected eye(s) twice a day (BID).

3. DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

4. CONTRAINDICATIONS
BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients [see Adverse Reactions (6.2)].

5. WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE® should not be used to treat contact lens-related irritation. BEPREVE® should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of of BEPREVE®.

5.3 Topical Ophthalmic Use Only
BEPREVE® is for topical ophthalmic use only.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience
The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely [two (2) possibly related cases for an incidence of 0.00006%] during the post-marketing use of BEPREVE®. Because this reaction is reported voluntarily from a population of unknown size, the actual incidence cannot be verified. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral does up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1000 mg/kg/day, however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3300 times the topical ocular use in humans). The concentration of radiolabeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

There are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

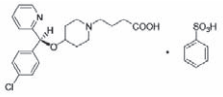
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radio-labeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 µg eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use
Safety and efficacy of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

8.5 Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11. DESCRIPTION
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE® contains 15 mg of bepotastine besilate. Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1 receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics
Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four time daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were the below quantifiable limit (2ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use.

The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for human topical use).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3300 times the systemic concentration anticipated for topical ocular use in humans).

14. CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE®.

The safety of BEPREVE® was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16. HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following sizes:

5 mL (NDC 67425-007-50)
10 mL (NDC 67425-007-75)

STORAGE
Store at 15° – 25°C (59° – 77°F).

17. PATIENT COUNSELING INFORMATION

17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE® should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE®.

Manufactured for: ISTA Pharmaceuticals, Inc.
Irvine, CA 92618

By: Bausch & Lomb Incorporated
Tampa, FL 33637

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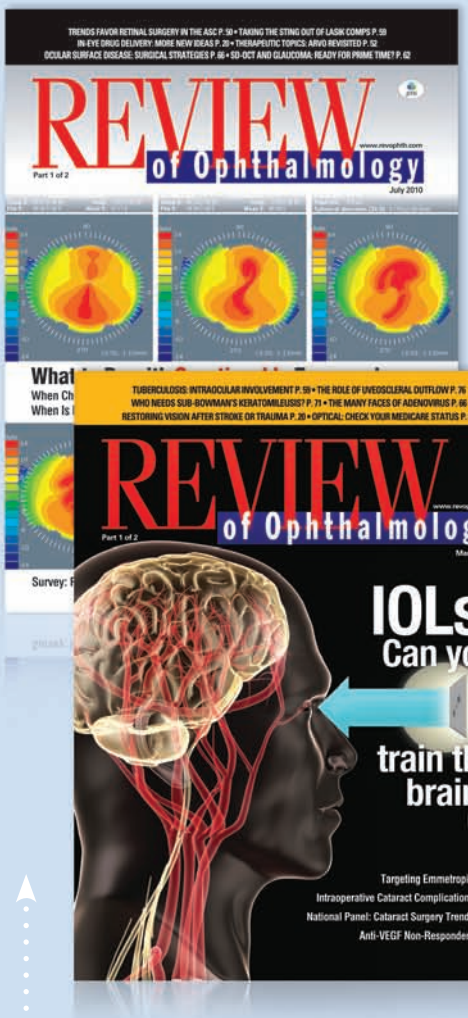

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Retinal Prostheses Offer Hope to Blind Patients

Two retinal prostheses are ahead of the field in their stage of development. Here's a look at how they work.

By Sunir Garg, MD, Philadelphia

Degenerative retinal diseases such as atrophic macular degeneration and retinitis pigmentosa can cause severe vision loss. While vision loss is devastating at any age, RP often affects working-age adults. The current treatment options are limited. Vitamins help slow disease progression. Visual cycle modulators are in clinical trials; initial experience suggests they slow disease progression and may improve vision in patients with mild to moderate disease. For blind patients with light perception, or even no light perception vision, retinal chip implants offer hope.

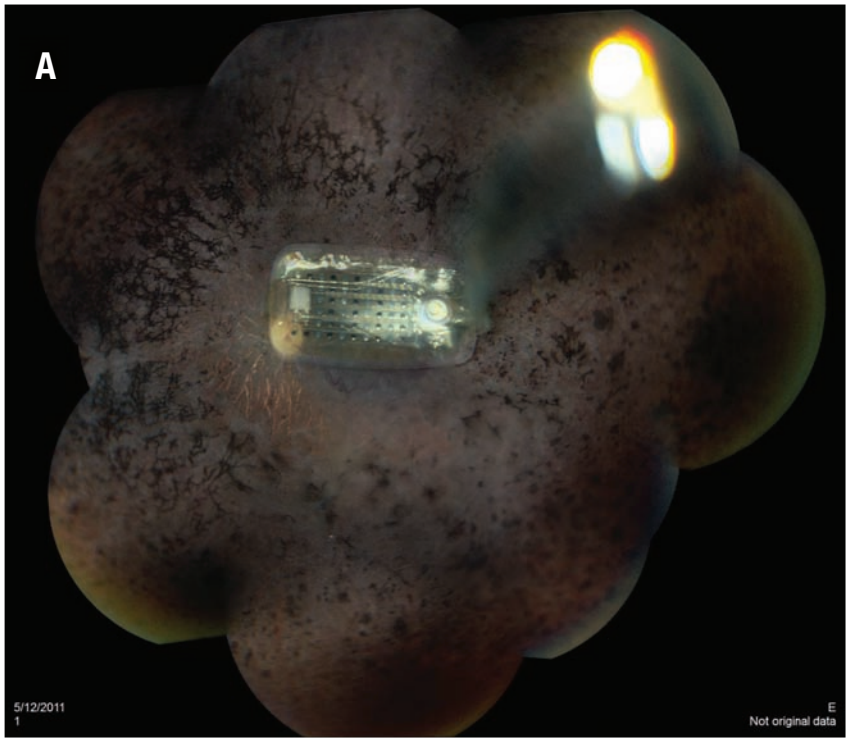


Figure 1A. The Argus II Implant attaches to the retinal surface with a tack. The cable that both powers the chip and conducts the image signal from the episcleral housing is seen temporally (on the right side of the photographs).

Background

RP is an outer retinal degeneration that affects the retinal pigment epithelium and the photoreceptors. Eyes with RP respond to electrical stimulation because in many patients, the inner retina and ganglion cell layer still have some function. The retinal chip implants stimulate these cells.

More than a dozen groups of investigators and companies around the world are working on retinal implants (Table 1). In order to restore visual function, chip implants have to detect light, convert the light energy to electrical energy, and then stimulate the retina. Different groups approach this in different ways.[1,2] This article focuses on two implants that are furthest along the path to clinical availability: the Argus II Implant by Second Sight and the Active Subretinal Implant by Reti-

This article has no commercial sponsorship.

nal Implant AG. The Argus Implant directly stimulates the ganglion cells. The Active Subretinal Implant recreates some of the signals that normally would have been made by the photoreceptors.

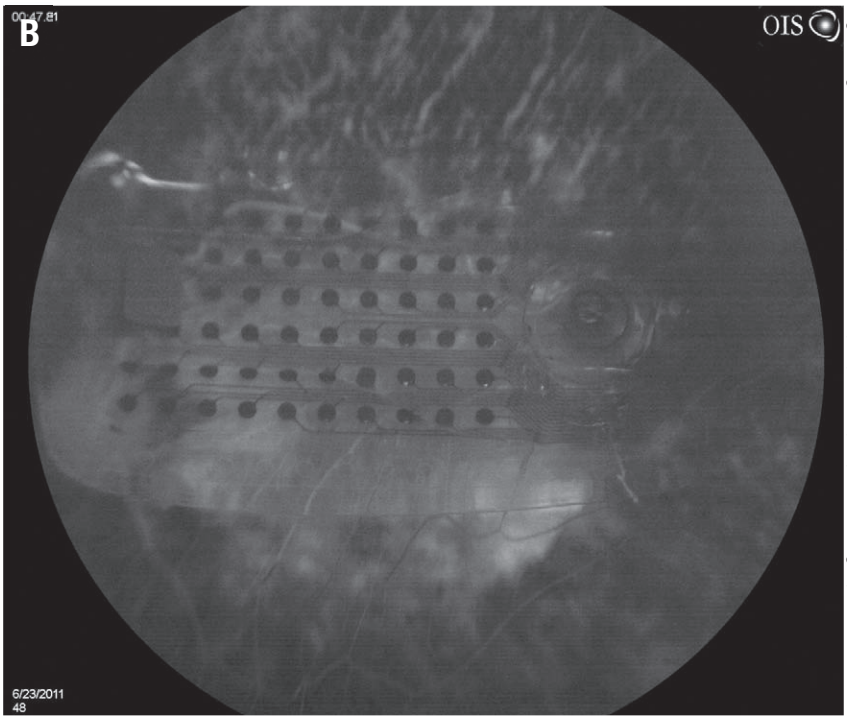
The Argus II Implant

Developed by Mark Humayun, MD, and colleagues at the Doheny Eye Institute, University of Southern California, the Argus II Implant has received a CE Mark in Europe and, this month, was granted approval by the U.S. Food and Drug Administration *(See Review News, p. 3)*. The Argus II epiretinal implant is a 60-channel electrode array that directly stimulates the ganglion cells.[3]

The Argus II Implant consists of four parts. The power comes from a battery pack worn on the hip. An external video camera wirelessly delivers images to the electrical housing that is affixed to the episclera (similar in some sense to the plate of a glaucoma filtering tube). The image and data processing are done here. A cable from the electrical housing enters the eye through an incision in the pars plana and the electrical impulses then are sent through the cable to the chip. The chip itself is attached to the retina with a tack *(See Figure 1A)*.

All 30 patients who received the implant during the trial were able to perceive light during stimulation. More than half of the patients were able to see the motion of a white bar moving across a black background. Many of the implanted patients were able to identify some 3 to 4.5 cm letters on a high-contrast background. The best vision to date was 20/1,262. These initial results are encouraging and will allow further refinement of the device.

There were a few adverse events. Approximately 10 percent of patients had conjunctival erosion over the implant. This was able to be repaired in all patients but one. Three cases of endophthalmitis and three cases of hypotony occurred, and all were successfully treated. One patient had to have the implant removed. One patient was found to have an intraoperative tear, and two patients developed post-procedure retinal detachments. These were all successfully repaired.



Argus images: Elaine Liebenbaum, Julia Haller, MD, Allen Ho, MD, and Carl Regillo, MD

Figure 1B. An early frame of a fluorescein angiogram in a patient with the Argus II Implant demonstrates some persistent macular perfusion.

One of the advantages of this implant is that it attaches directly to the ganglion cells, which are ultimately the cells that need to be stimulated to generate a visual signal that is then sent to the brain. As the electrode array becomes larger and/or is able to contain more electrodes, the cable might be able to be exchanged while keeping the electronic housing intact. From the patient's perspective, the main disadvantage is the use of an external camera. To scan an area, the patient has to move the camera (basically his head) around. The current implant has a limited number of electrodes so the images only have rudimentary shapes, but this will be improved in future iterations.

The Active Subretinal Implant

Developed by Eberhard Zrenner, MD, and colleagues at the University of Tubingen in Germany, the Active Subretinal Implant is currently in clinical trials in several European centers and in Asia. The device is under review by the FDA as an investigational device and once FDA approval is obtained, Wills Eye Institute will be the lead clinical trial site in the United States. This implant contains a 1,500-electrode array that directly stimulates the inner retina. In contrast to the Argus II implant, which bypasses the inner retina, the Active Subretinal Implant aims to replace the dysfunctional photoreceptors.

The Active Subretinal Implant contains photodiodes on the subretinal chip, so there is no camera. The light stimulation occurs similar to the way we see—the light coming from an object goes through the pupil and activates the implant, which then converts

Images: Retina Implant AG

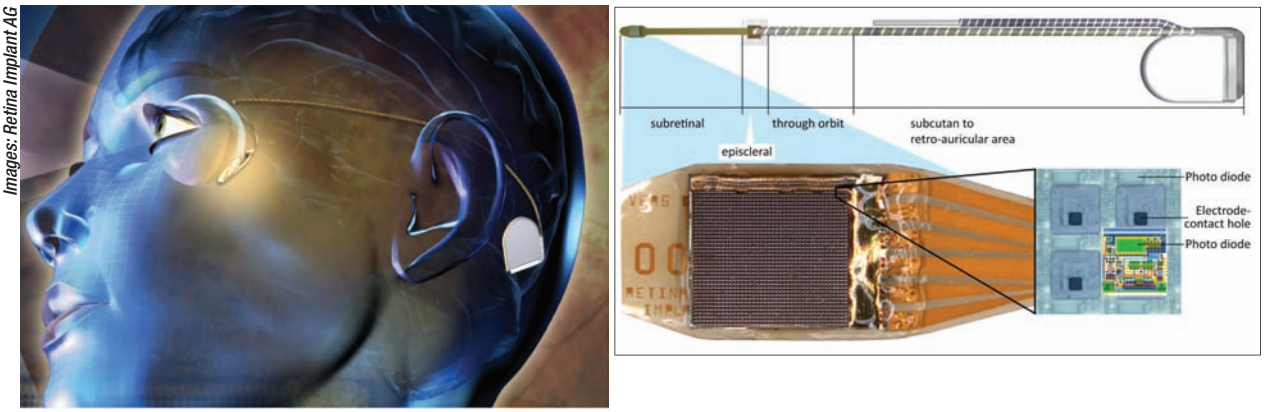


Figure 2. Left: The Active Subretinal Implant is powered by a handheld battery pack that transmits electrical energy to an inductive coil with magnet that is surgically implanted behind the ear; the connecting cable to the implant is tunneled under the skin toward the eye. Right: The implant has a 1,500-electrode array that both detects light and processes the image.

the light directly into electrical stimulation. In contrast to the epiretinal implant, the subretinal implant does the image processing within the chip itself. However, using this technology requires more energy than light can provide. This is provided via a handheld battery pack that also has controls for brightness and contrast. The necessary energy is transmitted transdermally via a receiver induction coil and a magnet that is implanted under the skin behind the ear. A subdermal cable tacked to the lateral canthus connects the receiver to the subretinal implant for energy.

There are published reports on a total of 21 patients who have received the subretinal 1,500-photodiode implant.[4,5] Patients receiving the subretinal implant have achieved VA of up to 20/1,000 within an 11 degree by 11 degree visual field. Functional outcomes included localization of objects of daily life such as plates and drinking glasses; increased mobility; motion detection; orientation in outside environments; recognition of facial details; even reading and detecting spelling errors in words written in letters 6-8 cm in size. Reports show that the implant can be safely removed and a new implant reinserted as the technology evolves. There have been no cases of endophthalmitis, two cases of conjunctival erosion, one case of retinal hemorrhage that cleared spontaneously, and one case of retinal detachment that was surgically repaired.

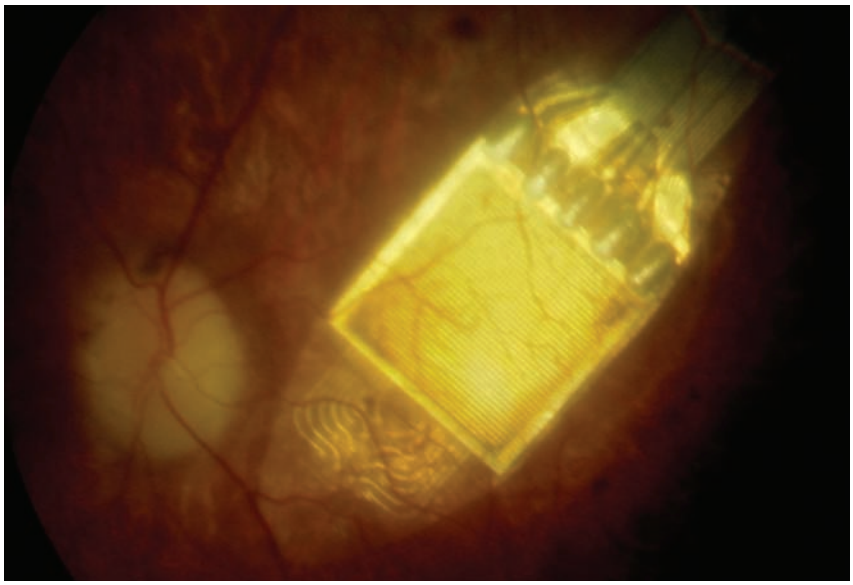
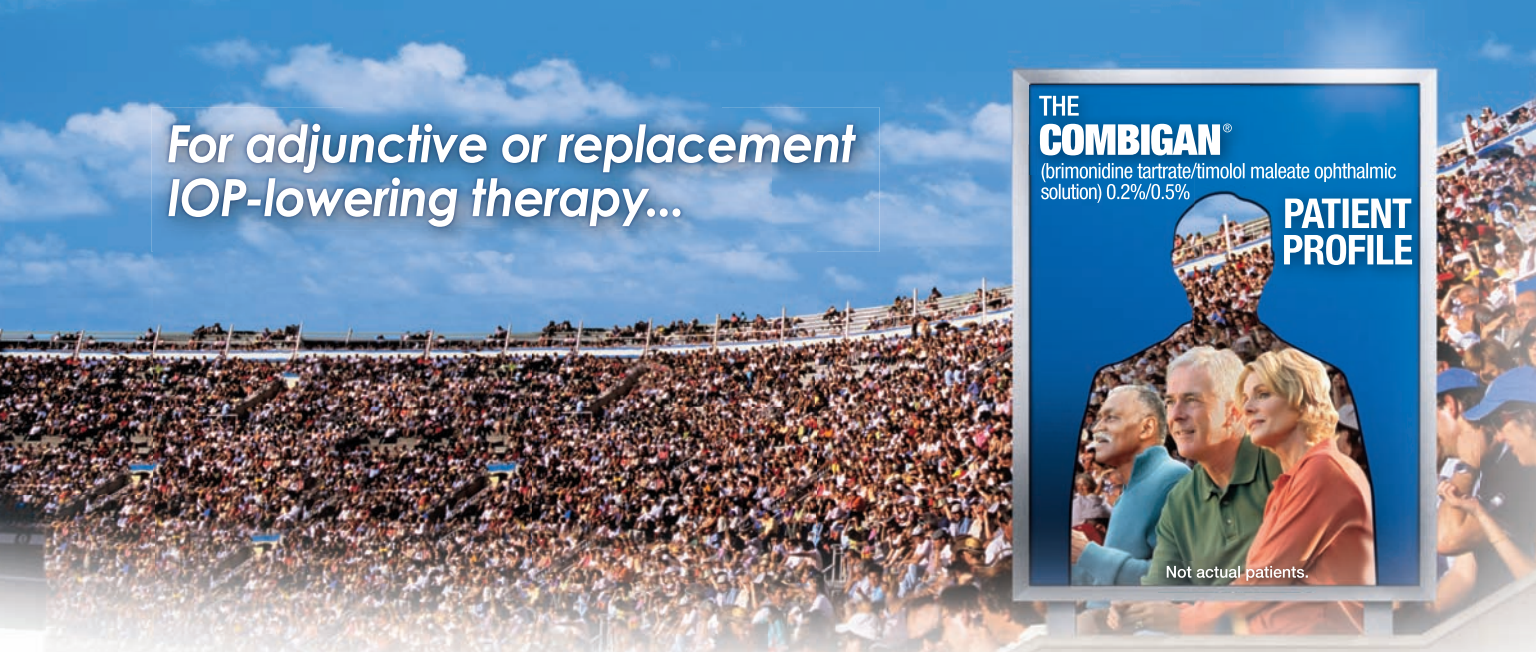


Figure 3. The Active Subretinal Implant is placed under the retina without the use of fixation devices such as a tack.

One of the main advantages of this subretinal implant is that, other tahn the battery pack, no hardware has to be worn by the patient. There is no external camera, so images are seen by moving the eye, and not the head. With 1,500 electrodes on the chip, it has the potential to give patients a higher-resolution image. While these results are encouraging, a larger cohort, with longer follow-up is needed.

Although both the Argus II Implant and the Active Subretinal Implant surgeries are somewhat complicated, both use techniques familiar to vitreoretinal surgeons.

The ability to integrate retinal implant technology into the human neural system to restore limited vision has not only been a major scientific advance, but also a positive life-changing experience for many of the selected patients in these limited clinical trials. The results of these trials, current and future engineering and technical advances, and the



Can More of Your Patients Benefit From the Power of COMBIGAN®?

INDICATIONS AND USAGE: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of COMBIGAN® dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: COMBIGAN® is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBIGAN® in the past.

WARNINGS AND PRECAUTIONS: COMBIGAN® contains timolol maleate. COMBIGAN® is administered topically, but can be absorbed systemically. The adverse reactions with systemic administration of beta-adrenergic blocking agents may occur with topical use (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported with systemic or ophthalmic administration of timolol maleate).

Sympathetic stimulation may be essential to support the circulation in patients with diminished myocardial contractility and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients with no history of cardiac failure, continued depression of the myocardium with beta-blocking agents over time can lead to cardiac failure. Discontinue COMBIGAN® at the first sign or symptom of cardiac failure.

Patients with chronic obstructive pulmonary disease (eg, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease should not receive beta-blocking agents, including COMBIGAN®.

COMBIGAN® may potentiate syndromes associated with vascular insufficiency. Use caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Patients taking beta-blockers with a history of atopy or 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.

Beta-adrenergic blockade can potentiate muscle weakness with myasthenic symptoms (eg, diplopia, ptosis, and generalized weakness). Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia and clinical signs (eg, tachycardia) of hyperthyroidism. Use caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients that may develop thyrotoxicosis to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Ocular hypersensitivity has occurred with brimonidine tartrate ophthalmic solutions 0.2% (eg, increase in IOP).

Some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

ADVERSE REACTIONS: The most frequent reactions with COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% in about 5% to 15% of patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.

DRUG INTERACTIONS: COMBIGAN® may reduce blood pressure. Use caution in patients on antihypertensives and/or cardiac glycosides.

Observe patients receiving a beta-adrenergic blocking agent orally and COMBIGAN® for additive effects of beta-blockade, both systemic and on intraocular pressure. Concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Use caution in the co-administration of beta-adrenergic blocking agents (eg, COMBIGAN®) and oral or intravenous calcium antagonists due to possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. Avoid co-administration in patients with impaired cardiac function.

Observe patients closely when a beta-blocker is administered to patients receiving catecholamine-depleting drugs (eg, reserpine) due to possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Specific drug interaction studies have not been conducted with COMBIGAN®, but consider the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics).

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

Potentiated systemic beta-blockade (eg, decreased heart rate, depression) has been reported with combined use of CYP2D6 inhibitors (eg, quinidine, SSRIs) and timolol.

Tricyclic antidepressants (TCAs) can blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of TCAs with COMBIGAN® in humans can interfere with the IOP-lowering effect. Caution is advised in patients taking TCAs, which can affect the metabolism and uptake of circulating amines.

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially increase systemic side effect such as hypotension. Use caution in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

Please see the Brief Summary of the full Prescribing Information on the next page.

Combigan®
(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

Write it RIGHT DAW

COMBIGAN®

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

BRIEF SUMMARY

Please see the **COMBIGAN®** package insert for full prescribing information.

INDICATIONS AND USAGE

COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of **COMBIGAN®** dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

CONTRAINDICATIONS

Asthma, COPD: COMBIGAN® is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease.

Sinus bradycardia, AV block, Cardiac failure, Cardiogenic shock: COMBIGAN® is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.

Neonates and Infants (Under the Age of 2 Years): COMBIGAN® is contraindicated in neonates and infants (under the age of 2 years).

Hypersensitivity reactions: Local hypersensitivity reactions have occurred following the use of different components of **COMBIGAN®**. **COMBIGAN®** is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

Potentiation of respiratory reactions including asthma: COMBIGAN® contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate.

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, **COMBIGAN®** 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 **COMBIGAN®** is contraindicated] should, in general, not receive beta-blocking agents, including **COMBIGAN®**.

Potentiation of vascular insufficiency: COMBIGAN® may potentiate syndromes associated with vascular insufficiency. **COMBIGAN®** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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.

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.

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.

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.

Ocular Hypersensitivity: Ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solutions 0.2%, with some reported to be associated with an increase in intraocular pressure.

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.

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.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **COMBIGAN®:** In clinical trials of 12 months duration with **COMBIGAN®**, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

Other adverse reactions that have been reported with the individual components are listed below.

Brimonidine Tartrate (0.1%-0.2%): Abnormal taste, allergic reaction, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), hordeolum, insomnia, keratitis, lid disorder, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, taste perversion, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity. **Timolol (Ocular Administration):** *Body as a whole:* chest pain; *Cardiovascular:* Arrhythmia, bradycardia, cardiac arrest, cardiac failure, cerebral ischemia, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, Raynaud's phenomenon, syncope, and worsening of angina pectoris; *Digestive:* Anorexia, diarrhea, nausea; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; *Skin:* Alopecia, psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and generalized and localized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, nasal congestion, respiratory failure; *Endocrine:* Masked symptoms of hypoglycemia in diabetes patients; *Special Senses:* diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus; *Urogenital:* Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

Postmarketing Experience: Brimonidine: The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions. **Oral Timolol/Oral Beta-blockers:** The following additional adverse reactions 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:* Decreased exercise tolerance, extremity pain, weight loss; *Cardiovascular:* Vasodilatation, worsening of arterial insufficiency; *Digestive:* Gastrointestinal pain, hepatomegaly, ischemic colitis, mesenteric arterial thrombosis, vomiting; *Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Increased pigmentation, pruritus, skin irritation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometrics, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly clouded sensorium, vertigo; *Respiratory:* Bronchial obstruction, rales; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides: Because **COMBIGAN®** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **COMBIGAN®** is advised. **Beta-adrenergic Blocking Agents:** Patients who are receiving a beta-adrenergic blocking agent orally and **COMBIGAN®** 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 co-administration of beta-adrenergic blocking agents, such as **COMBIGAN®**, 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. **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. **CNS Depressants:** Although specific drug interaction studies have not been conducted with **COMBIGAN®**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. **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. **Tricyclic Antidepressants:** Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **COMBIGAN®** in humans can lead to resulting interference with the IOP-lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. **Monoamine oxidase inhibitors:** Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with **COMBIGAN®** 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] 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 1,000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **COMBIGAN®** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **COMBIGAN®** 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: COMBIGAN® is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of two years.

The safety and effectiveness of **COMBIGAN®** have been established in the age group 2-16 years of age. Use of **COMBIGAN®** in this age group is supported by evidence from adequate and well-controlled studies of **COMBIGAN®** in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

OVERDOSAGE

No information is available on overdosage with **COMBIGAN®** in humans. There have been reports of inadvertent overdosage with timolol 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. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

Rx Only

APC33KM13

Based on package insert 72060US13 revised 10/2012.

ALLERGAN®

Table 1. A Sampling of Research on Visual Prostheses Around the World

Company and/or University	Principal Investigator	Location	Type of implant	Status
Retina Implant AG	Eberhart Zrenner	University of Tubingen, Germany	Subretinal	Human trials ongoing
Optobionics	Alan and Vincent Chow	Chicago	Subretinal	Human trials performed, further study on hold; Company reorganizing
Boston Subretinal Implant Project	Joseph Rizzo and John Wyatt	Harvard and MIT	Subretinal	Preclinical
Stanford University	Daniel Palanker	Stanford University	Subretinal	Preclinical
Seoul National University	J.-M. Seo	Seoul, Korea	Subretinal	Preclinical
Bionic Vision Australia	Anthony Burkitt	University of Melbourne, Australia	Suprachoroidal	Human trials just started
The Visual Prosthesis Project	Nidek, Japan	Nidek, Japan	Suprachoroidal	Human trials ongoing
Second Sight	Mark Humayun	University of Southern California	Epiretinal	FDA approval pending, CE Mark granted
IMI GmbH	IMI Devices	Bonn, Germany	Epiretinal	Human trials started; Company closed
Epi-Ret3	Peter Walter	Aachen University, Germany	Epiretinal with IOL-type receiver	Human Trials stopped; Company closed
Australian Vision Prosthesis Group	Nigel Lovell and Gregg Suaning	University of New South Wales, Australia	Epiretinal with sensor in anterior segment	Preclinical
NanoRetina	Yossi Gross and Jim Von Her	BioRetina, Israel	Epiretinal	Preclinical
Japan Visual Prosthesis Project	Tohru Yagi	Tokyo Intitute of Technology, Japan	Biohybrid using regenerated neurons	Preclinical
Tohoku University	Hiroyuki Kurino and Hiroshi Tomita	Japan		Preclinical
BrainPort Technologies	Wicab, Inc	Middleton, Wis.	Epilingual	Human trials ongoing
Cortivus	Eduardo Fernandez	Universidad Miguel Hernandez, Spain	Cortical	Preclinical
Utah Visual Prosthesis	Richard Norman	University of Utah	Cortical	Preclinical
Intracortical Visual Prosthesis	Philip Troyk	Illinois Institute of Technology	Cortical	Preclinical
Polystim Neurotechnologies	Mohamed Sawan	Ecole Polytechnique de Montreal	Cortical	Preclinical
Implantable Multi-contact Active Nerve Electrode	Jean Delbeke	University Catholique de Louvain, Belgium	Optic nerve	Preclinical

A number of groups around the world are working on visual prostheses of all types, including some on the tongue, optic nerve and brain. (This table is not intended to be an all-inclusive listing.)

evolving adaptive ability of patients learning to resume normal activities of daily living offer hope for our blind patients. REVIEW

Dr. Garg is an associate professor of ophthalmology at the Retina Service of Wills Eye Institute, and is a partner with MidAtlantic Retina. He can be reached at sgarg@midatlanticretina.com.

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The Pillars of Ocular Surface Pathology

An in-depth look at the two conditions common to many patients: allergic conjunctivitis and dry eye.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, PhD, Andover, Mass.

Two conditions we deal with frequently are allergic conjunctivitis and dry eye. Each presents with a spectrum of symptomatology and, although treatments are available for both, there is also room for therapeutic improvement. A key area of unmet need is the intersection of these two conditions, with the growing awareness that as the prevalence of each condition rises, many patients experience both ocular allergy and dry eye.

Although population demographics suggest that there is likely to be a high degree of comorbidity between allergy and dry eye, there are few direct studies that address this issue. Two large-cohort, longitudinal studies do provide evidence that these are not simply two separate, independent conditions.[1,2] Data from both of these studies indicates that patients who suffer from allergic conjunctivitis are significantly more likely to experience signs and symptoms of dry-eye disease, especially as they reach middle age. Despite their distinct underlying etiologies, both conditions can lead to a chronic state of ocular surface inflammation and discomfort, which can ultimately result in significant visual dysfunction.

Ocular allergies, including both seasonal and perennial varieties, affect an estimated 60 million people in the United States and between 20 and 30 percent of individuals throughout the rest of the industrialized world.[3] A combination of pollution and a growing urban lifestyle has contributed to the trend of increased prevalence of allergic disease over the past half-century. Additional factors, including climate change, are thought to contribute to this trend by enhancing conditions for pollen production.[4] The spectrum of allergic rhino-conjunctivitis represents a key aspect of what clinicians and researchers have called the atopic march, or the tendency for individuals to experience a progressive series of allergic conditions, from dermatitis to allergic conjunctivitis to rhinitis and then to asthma, over the course of their lives.

While atopy continues its relentless march, the increased lifespan and the aging of populations worldwide are contributing to increased dry-eye prevalence. Like ocular allergy, dry eye is a disorder that ranges from a minor inconvenience to a pervasive, life-altering affliction. It is a condition more common in women, and more common in patients over 50.[5] Dry eye differs from ocular allergies, however, in that it has an extremely heterogeneous etiology that includes Sjögren's syndrome, meibomian gland disorders and neural loop disorders that interfere with reflex tearing. Other causes include various dyslipidemias, mucin disorders (including cystic fibrosis), Stevens-Johnson syndrome and the keratitis that can sometimes occur following refractive surgery.[5] Environmental factors play a key role in disease presentation, and many such factors (humidity, air flow and visual tasking) can lead to a significant exacerbation of dry-eye symptoms.

Both ocular allergy and dry eye are aggravated by atmospheric pollutants such as ozone, automobile emissions and other byproducts of fossil fuel combustion. Ozone exposure can lead to elevated free radical damage to proteins and other cell constituents on the ocular surface. Other emission compounds can act as antigens, stimulate immune responses to other airborne allergens, or act as direct irritants to the ocular mucus mem-

This article has no commercial sponsorship.

branes they contact, eliciting both lacrimation and immune responses. This is just one example of the close association between these two ocular disorders; the report of the International Dry-eye Workshop listed allergic conjunctivitis as a key "extrinsic factor" in dry-eye etiology.[5] Despite this, there has been little focus on the causal relationships and the potential for overlapping, synergistic therapies for the two conditions, to date.

One aspect of the comorbidity that does seem to be emerging is the reduced seasonality of the combined disorders. Dry-eye patients typically experience more severe symptoms in winter months when humidity is lower and people spend more time indoors.[5] The majority of patients with allergies are symptomatic in spring or fall, depending upon the specific allergens to which they respond.[3] In contrast, those with both dry eye and allergies are more likely to experience year-round ocular symptoms. This may reflect a greater proportion of patients with perennial allergies, or may simply be due to the combined assault of both conditions on the ocular surface.

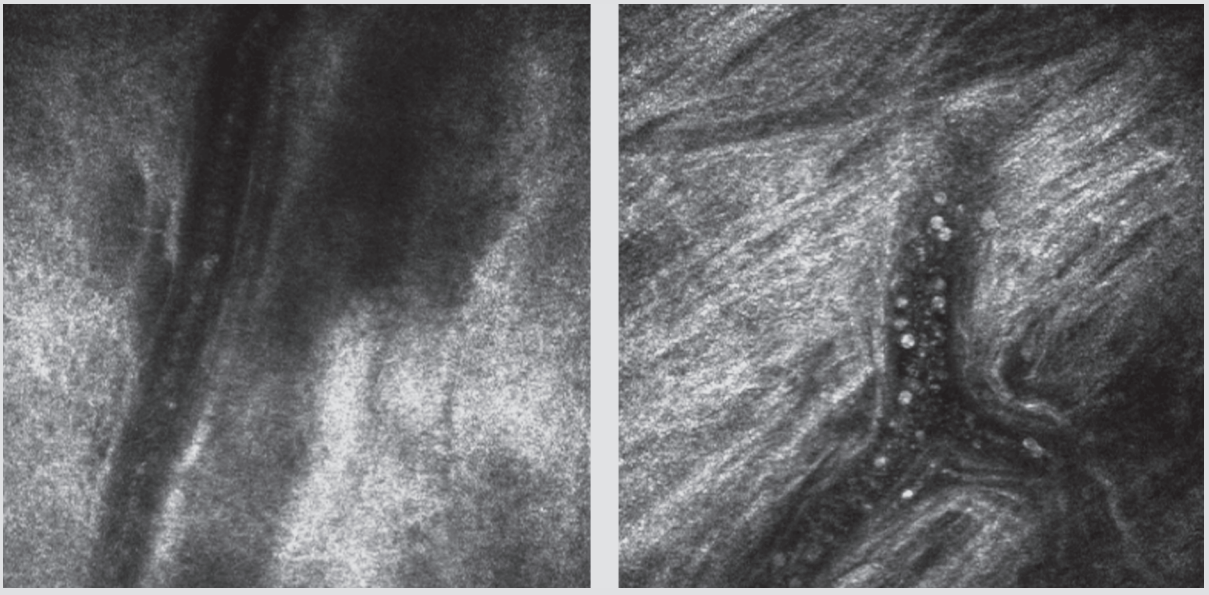
Both allergic conjunctivitis and keratoconjunctivitis sicca are aggravated by pollutants in the atmosphere, including ozone, emissions from cars and trucks, and the various by-products of fossil-fuel combustion.

Treating the Comorbid Patient

The starting point for therapy of both conditions is likely to include the use of tear substitutes, which can flush allergens from the ocular surface while at the same time replenish a shortage of tear volume. Over-the-counter oral antihistamines might be an option for treating ocular allergies, but some of these come with a particularly troublesome side effect: The relief they provide from allergies is offset by their tendency to exacerbate symptoms of dry eye. A number of studies have shown that oral antihistamines such as loratadine or cetirizine can reduce aqueous tear production and worsen the ocular burning, grittiness and corneal staining in patients who suffer from dry eye.[6,7] Another recent study examined tear composition in patients with allergic conjunctivitis, and found that changes resulting from allergies could contribute to tear-film instability.[8] Thus it appears that allergies may predispose patients to developing dry-eye disease in a number of ways.

Beyond the use of artificial tears, treatment options for both conditions overlap with the use of topical or systemic anti-inflammatories such as corticosteroids. In addition, several recent studies have suggested that some dual-action topical antihistamines, notably olopatadine and alcaftadine, may also exhibit some degree of anti-inflammatory effects.[9,10] When tested in preclinical models of dermal inflammation, olopatadine inhibits cytokine levels while also inducing secretion of hyaluronic acid, a compound involved in epidermal healing.[9] Alcaftadine is known to exert stabilizing effects on epithelial tight junctions that can mitigate the movement of pollens or other allergens into the ocular epithelium.[10] Alcaftadine also has a mixed antihistamine antagonism (it inhibits H1, H2 and H4 receptors *in vitro*),[11] an action that may be useful in direct inhibition of basophils.[12] The pleiotropic actions of these drugs provide the basis for their use in patients with ocular allergies who also suffer from dry-eye disease.

Topical corticosteroids such as loteprednol are the last resort for both allergy and dry eye, and when used judiciously these agents can safely break the inflammatory momentum that can result from either of these conditions, whether the condition is in isolation or exists in combination with the other. As long as the duration of steroid therapy is kept within a one- to two-week window the risks of increased intraocular pressure or ocular infection should not become significant. The other therapy used for dry eye, cyclosporine, is a drug with multiple actions that relieves dry eye by enhancing aqueous tear production in approximately 12 to 15 percent of patients.[13] Despite this, neither cyclosporine nor any related drug (such as tacrolimus) appears to hold promise as a universal therapy for other ocular inflammatory conditions, including allergy or allergy plus dry eye.



Confocal video microscopy provides images of the conjunctival surface before (left) and after (right) allergen challenge. The infiltration of inflammatory cells seen after the allergen challenge is characteristic of both late-phase allergy and dry-eye disease.

Addressing Unmet Needs

While patients with ocular allergies experience an increased risk for dry eye, the converse is also true: Dry eye can exacerbate allergic signs and symptoms. In a recent paper we described a study that tested effects of exposure to an adverse environment designed to evoke dry eye (using the Ora Controlled Adverse Environment model) on the allergic responses of patients who report suffering from both allergic conjunctivitis and dry eye.[14] The adverse environment model caused a significant increase in all measures of acute allergic conjunctivitis. Using confocal microscopy of the patients' conjunctival surface, we were able to show that these increases in allergic response coincided with increases in the number of inflammatory cells infiltrating the conjunctival vasculature.

Two additional recent studies document damage to the conjunctival and corneal epithelium associated with prolonged allergen exposure[10,15] and describe an ocular surface disease that is remarkably similar to that seen in dry eye. Future efforts in therapeutic development may well be designed to treat both conditions by addressing this underlying inflammatory nature.

Historically, the stumbling block for dry-eye drug development has been the apparent disconnect between signs and symptoms of dry-eye disease—dry-eye patients may be asymptomatic with significant corneal pathology, or may suffer from severe burning and ocular discomfort with little or no corneal staining in the clinic. The search for reliable biomarkers for ocular surface pathology is aimed at providing a reliable metric for drug discovery.[16] Potential targets for this quest include tear components such as cytokines, mucins, lipids or metalloproteinases. Others include quantifying conjunctival cell types or parameters derived from impression cytology.[17] Based on the underlying inflammatory etiology, reliable dry-eye markers should also be valuable in developing treatments for late-phase allergy and for the combination of allergy and dry eye.

As we learn more about the pathology of the ocular surface, the commonalities between tear-film dysfunction and allergic disease become more apparent. While the pathological processes underlying disease in each patient represent a complex amalgam of genetic, molecular and environmental factors, the end result seems to include a robust complement of signs and symptoms common to many patients with dry eye, allergy or both. The shared changes in the ocular surface include structural modifications in the epithelial cells, inflammatory cell infiltration and inflammatory mediator release, as well as alterations in tear constituents. Each of these variations from the normal ocular surface homeostasis contributes to expression of the disease phenotype, and each represents a potential target for therapeutic intervention.

As with all new treatments, the key to addressing the needs of this growing population of patients is establishing viable metrics and efficacy standards for therapeutic development. Ideally, new treatments will provide

relief to sufferers of both dry eye and allergy, so symptoms of either disease need not be overlooked. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute. Dr. McLaughlin is a medical writer at Ora Inc.

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Refractive Surgery and The Dry-eye Patient

Many eyes can be rehabilitated before surgery, say surgeons, but you still have to be vigilant for intractable cases.

Walter Bethke, Managing Editor

Surgeons say that dry-eye disease after LASIK is one of the most miserable complications patients can experience, and managing it often involves a lot of patient stress, handholding, chair time and sheer recovery time. In light of this, surgeons say that when a patient with dry eyes comes into their office requesting laser vision correction, they have their work cut out for them, since they don't want to make a moderate condition bad or a bad condition worse. Here, experienced refractive surgeons weigh in on their approach to these patients.

Assessing the Dry Eye

Since the postop stakes are high if a patient develops bad dry eye, surgeons make sure to root out any preop dry eye and its cause.

"There's not one test that gives you the answer, but instead it's a variety of factors that you put together," says Christopher Rapuano, MD, Wills Eye Institute cornea and external disease director. "If I had to pick one, though, it would be determining how symptomatic they are from dry eye. Many people who get laser vision correction were contact lens wearers for many years and did fine. Then, their eyes got a little on the dry side and they couldn't comfortably wear their contacts anymore because their eyes got red and irritated. So, they stopped wearing contact lenses and came to see you about refractive surgery. You have to ask these patients why they stopped wearing contacts. If they say that they just didn't like to put them in anymore, or they got an infection and became too scared to keep wearing them, that's one thing. But if they say their eyes were bone dry and irritated when they put their contacts in, that's a clue that they've got some dryness issues and they're at higher risk. And this is a reasonable number of patients.

"For those higher-risk patients, I'll go more in-depth with my tests," Dr. Rapuano continues. "This includes performing tests like lissamine green staining and Schirmer's, which I don't do on everyone."

Teaneck, N.J., corneal specialist Peter Hersh also tries to discriminate between patients who are just contact lens-intolerant and those with physiologic dry eye, and then relies on a thorough exam. "More often than not, the dry eye is secondary to blepharitis or inflammation secondary to blepharitis," he says. "So I'll check to see whether the patient has lid margin changes or inspissation of the meibomian glands. I'll evert the lids to see if there's a follicular reaction, especially to contact lenses. Then I turn to the conjunctiva and cornea. I first evaluate the tear film, the tear-film breakup time—which we do in all patients—and certainly look for any staining with fluorescein. Questions I consider are: Is there any superficial punctate keratitis? If there is, is it localized? Is it more of an inferior thing that might be secondary to a blepharitis? I can use the last question in my blepharitis analysis, as well. Often, the SPK will be inferior and associated with blepharitis."

The staining pattern, both initially and on follow-up after some dry-eye treatment, can be very helpful when deciding if someone is a candidate for LVC. "If there's pan-SPK and staining of the conjunctiva, that's a real red flag that the patient has a real dry-eye pathology," avers Dr. Hersh. "Those are the kinds of patients we might not be

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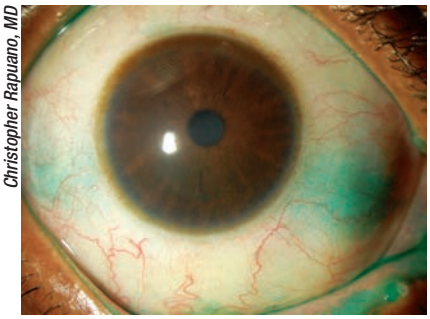
able to treat and get in good-enough shape to proceed with LVC."

Rehabilitating the Eye

After they've assessed the patient's dry eye, physicians then embark on a course of treatment and will follow-up with the patient to see if it's made a difference in the disease.

Sadeer Hannush, MD, attending surgeon on the cornea service at Wills Eye Institute and assistant professor of ophthalmology at Jefferson Medical College in Philadelphia, says that for patients who are simply dry, he'll "prepare them by inserting a plug in their inferior punctum and possibly putting them on Restasis twice daily a few weeks before surgery." However, he'll treat more involved conditions in different ways. "There are various ways of managing lacrimal deficiency: tear supplementation; punctal occlusion; reinvigorating the lacrimal gland with anti-inflammatory agents such as loteprednol or cyclosporine," he says. "On the other hand, in the case of evaporative dry eye due to meibomian gland dysfunction, which causes inflammation of the lid margins and prevents oil from covering the tear film, the treatment historically has been lid hygiene, warm compresses, oral doxycycline and the occasional use of anti-inflammatories. There are also new techniques, such as azithromycin drops, which work through a different mechanism in rehabilitating the lid margins, or the LipiFlow device that drains the meibomian glands and opens the pores, creating a healthy surface for a period of time." Dr. Hersh will also consider adding omega-3 fatty acid supplements to the blepharitis treatment.

For the patients who need such treatment before LVC, as opposed to those who are just a little dry, Dr. Rapuano will check back with them one to three months after initiating the treatment. "After a month or so, I'll perform some staining again and may do Schirmer's," he says. "The amount of observed staining is important. If they have significant staining—and dry eye tends to be in the middle to lower third of the cornea—and it looks like there's still dry eye, then we won't perform LVC on them. I tell them that, if their corneal and conjunctival surfaces are normal, I'll do refractive surgery on them. If it's never normal, then I'll never do surgery on them."



Christopher Rapuano, MD

In some patients with dry eyes, surgeons say preop punctal plugs (lower right in image) can help get the ocular surface ready for surgery.

LASIK or Surface Ablation?

Because lamellar procedures sever corneal nerves while surface ablations leave them intact, some surgeons feel that, in borderline cases, surface ablation might be preferable. Surgeons are quick to add that this is more of a clinical impression than one supported by the literature.

"I personally tend to avoid LASIK in patients who have dryness issues just because most of the bad dry-eye patients I've seen after LVC have been after LASIK," says Dr. Rapuano. "However, it's true that more people have had LASIK, so it's not a fair comparison. Personally, I think LASIK has a higher tendency to cause problems. However, a recent study by Edward Manche showed that, at one year, symptoms of dry eye, visual fluctuations and foreign body sensation returned to baseline in both LASIK and PRK eyes in the study.[1] So, there's reasonable data that one doesn't cause more dryness than the other, but that they both cause some dryness."

Some surgeons argue that LASIK can be made more gentle on the corneal nerves by using a nasal hinge, since the nerve plexus is denser nasally and temporally than it is superiorly or inferiorly. "My position, however," says Dr. Hannush, "is if a patient has dry eye—and is my mother or sister—I'd opt to preserve the entire nerve plexus and just do a surface procedure." Dr. Rapuano says a thinner flap might also be better for the same reasons, since it cuts fewer corneal nerves.

Dr. Hersh says, though, that he's not sure there's a difference. "In some cases, I'm more concerned that dryness will influence the quality of the epithelial healing after PRK than I am that the LASIK flap will exacerbate the dryness," he says.

Dr. Rapuano says that, whichever procedure is chosen for patients who are deemed suitable, there will be those who still have dry-eye problems postop, and need your attention. "In the case of any patient with complications, surgeons tend to not want to see them and be reminded that some patients are unhappy," he says. "It's a natural reaction, really, but surgeons need to overcome it and overcompensate for it. They need to see these patients more frequently if they want to be seen, and schedule them for the beginning or end of the day when the physician has more time for them and isn't rushed. Patients want to know that you're trying to help them, whether you did the surgery or someone else did. Tell them that you understand that they've got dry eye, you're doing your best to help them and that, fortunately, it usually gets better over three, six or 12 months." REVIEW

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Blind Subjects Detect Motion with Argus II

Results of a Phase I/II feasibility study of the 60-electrode Argus II retinal prosthesis system show that 54 percent (n=15) of blind subjects implanted with the prosthetic were able to perform a motion detection task they could not do with their native vision. This confirms that electrical stimulation of the retina provides spatial information from synchronized activation of multiple electrodes.

Twenty-eight blind subjects (bare light perception or worse in both eyes) with retinitis pigmentosa were implanted with the Argus II. The experiment measured patient ability to detect the motion of a high-contrast moving bar on a flatscreen monitor in three conditions: with the prosthesis system on and a one-to-one mapping of spatial information; with the system off; and with the system on with randomly scrambled spatial information.

Fifteen subjects performed the task better with their prosthesis system than with their residual vision. Two subjects had better performance with their residual vision while no difference was found for the remaining 11 patients. Of the 15 better-performing subjects, 11 were available for follow-up testing, and 10 had significantly better performance with normal rather than scrambled spatial information.

JAMA Ophthalmol 2013;131:2:183-189.

Dorn J, Ahuja A, Caspi A, de Cruz L, et al.

EBAA Does Not Recommend Antifungal Donor Storage Media

After reviewing adverse reactions reported to the Eye Bank Association of America through an online adverse reaction reporting system, the EBAA has determined that while there has been a nonsignificant increasing trend in the rate of fungal infection after corneal transplant, it is not sufficiently compelling to pursue antifungal supplementation of donor storage media.

Adverse reactions reported between January 1, 2007 and December 31, 2010 were reviewed to identify cases of recipient fungal infection. Data regarding the donor, donor cornea, recovery and processing, mate culture and clinical course of the recipients was collected. Out of 221,664 corneal transplants performed using corneal tissue distributed by domestic eye banks, 31 cases of culture-proven fungal keratitis (n=14) and endophthalmitis (n=17) were reported (1.4 cases per 10,000 transplants performed).

Fungal infections were more commonly reported after endothelial keratoplasty procedures (0.022 percent) than penetrating keratoplasty procedures (0.012 percent), but the difference was not statistically significant (p=0.076). No association was found between fungal infection after endothelial keratoplasty and whether the lamellar tissue cut was performed by the surgeon or the eye bank technician. Seventy-three percent (16 of 22) of the fungal cultures performed on the mate corneas were positive, with infection developing in 67 percent (10 of 15) of recipient eyes (endophthalmitis in six and keratitis in four eyes).

Cornea 2013;32:149-154.

Aldave A, DeMatteo J, Glasser D, Tu E, et al.

Evaluation of Corneal Astigmatic Marking Methods

In a randomized, examiner-masked clinical trial in Austria, doctors compared four devices used to mark the cornea before astigmatism-reducing surgery, determining that all the devices showed a slight deviation to the horizontal reference meridian. Because small deviations of the meridian can result in a relevant reduction in the astigmatism-reducing effect with toric intraocular lenses, accurate marking of the cornea before surgery is critical due to the variable cyclotorsion caused by a change from the upright to the supine position.

Patients (n=60) were randomly allocated to one of four groups for preoperative corneal marking in the sitting position. The four methods used were marking at the slit lamp with an insulin needle, a pendular marker, a bubble marker and a tonometer marker. The marks were then docu-

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mented with a standardized photographic technique, and the rotational deviation and vertical misalignment were assessed.

The pendular-marking device showed the least rotational deviation to the reference meridian (mean 1.8 degrees). There was no statistically significant difference between slit-lamp marking and pendular marking (p=0.05); however, there was a significant difference between the pendular marker and the bubble marker and between the pendular marker and the tonometer marker (p=0.01 and p<0.01). The least vertical misalignment was observed with the slit lamp-marking device (mean 0.28 mm). There was no statistically significant difference in vertical misalignment between the four groups.

J Cataract Refract Surg 2012;38:2094-2099.
Popp N, Hirnschall N, Maedel S, Findl O.

Wavefront Sensor Excellent at Measuring HOAs

Researchers in Spain assessed the intrasession and intersession precision of ocular, corneal and internal higher-order aberrations measured using an integrated topographer and Hartmann-Shack wavefront sensor (Topcon KR-1W) in refractive surgery candidates. The intrasession repeatability was high; therefore, the device's ability to measure HOAs in a reliable way was excellent. Under intersession reproducibility conditions, dependable corneal spherical aberration measurement were provided.

In order to measure intrasession repeatability, one experienced examiner measured eyes nine times successively. To study intersession reproducibility, the same clinician obtained measurements from another set of eyes in two consecutive sessions one week apart. Ocular, corneal and internal HOAs were obtained. Coma and spherical aberrations, 3rd- and 4th-order aberrations and total HOAs were calculated for a 6 mm pupil diameter.

For intrasession repeatability (75 eyes), excellent intraclass correlation coefficients were obtained (ICC>0.87), except for internal primary coma (ICC=0.75) and 3rd-order (ICC=0.72) HOAs. Repeatability precision (1.96 x S_W) values ranged from 0.03 µm (corneal primary spherical) to 0.08 µm (ocular primary coma). For intersession reproducibility (50 eyes), ICCs were good (>0.8) for ocular primary spherical, 3rd-order and total higher-order aberrations; reproducibility precision values ranged from 0.06 µm (corneal primary spherical) to 0.21 µm (internal 3rd order) with internal HOAs having the lowest precision (≥0.12 µm). No systemic bias was found between examinations on different days.

J Cataract Refract Surg 2013;39:242-249.
López-Miguel A, Martinez-Almeida L, González-Garcia M, Coco-Martin M, et al.

A.M. Dose of Once-daily Glaucoma Rx More Convenient

Canadian researchers have determined that patients prefer morning administration of once-daily glaucoma medications to evening administration. While adherence decreases from the first to second month after initiation of treatment, recommending morning administration to patients may lead to greater medication adherence.

Thirty patients newly diagnosed with glaucoma or ocular hypertension requiring IOP reduction were started on travoprost eye drops and randomized to either morning or evening administration for one month. They were then crossed over to the opposite dosing schedule for the following month. Adherence was monitored using an automated dosing aid, and compared between morning and evening dose and first vs. second month dosing. Demographic characteristics were obtained and treatment effects were measured; patients also completed a post-study questionnaire regarding the convenience of the two dosing regimens.

Overall patient adherence was good (89.3 percent), and there was no statistically significant difference (p=0.07) in adherence between morning dosing (90.9 percent) and evening dosing (87.3 percent). Adherence in the first month (91.7 percent) was superior to the second month (86.5 percent). There was no significant difference in IOP response between morning and evening dosing.

J Glaucoma 2013;22:1-4.
Ford B, Gooi M, Carlsson A, Crichton A.

SD-OCT Use Shortens Duration Of Postop Prone Positioning

A retrospective review of patients with macular holes undergoing 23-ga. pars plana vitrectomy and intraocular gas tamponade concludes that confirming early closure of macular holes with spectral domain optical coherence tomography imaging can serve as an important guide to significantly shortening the duration of patient prone positioning while maintaining a high closure rate.

SD-OCT was done postop day one. Patients remained face down for two more days if the macular hole was closed, or six more days if the macular hole was open or indeterminate. There were eight Stage 2, 12 Stage 3 and 12 Stage 4 macular holes. On postop day one, 24 holes were confirmed closed by SD-OCT and patients were instructed to remain facedown for two more days. Twenty-three of the 24 holes remained closed. Eight holes were open or indeterminate on postop day one, and the patients remained face down for six more days. Six of the eight holes (75 percent) were closed at their last follow-up. The overall closure rate was 29/32 (90.6 percent), with an average follow-up of 334 days.

Retina 2013;33:356-362.
Shah S, Manjunath V, Rogers A, Baumal C, et al.

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*Post-hoc analysis of combined data from two studies using a contralateral conjunctival allergen challenge (CAC). Based on a scale of itching scores of 0-4, with 0 as no itching and 4 as severe itching. Ocular itching was evaluated 3 minutes after allergen challenge at onset and at 16 hours. †(N=85; 95% CI=48.8, 70.5) ‡(N=82; 95% CI=48.3, 70.4)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: PATADAY™ solution is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis.

DOSAGE AND ADMINISTRATION: The recommended dose is one drop in each affected eye once a day.

DOSAGE FORMS AND STRENGTHS: Ophthalmic solution 0.2%: each ml contains 2.22 mg of olopatadine hydrochloride.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: For topical ocular use only: not for injection or oral use. **Contamination of Tip and Solution:** As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Contact Lens Use: Patients should be advised not to wear a contact lens if their eye is red. PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

ADVERSE REACTIONS: Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%. The following ocular adverse experiences were reported in 5% or less of patients: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus. The following non-ocular adverse experiences were reported in 5% or less of patients: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion. Some of these events were similar to the underlying disease being studied.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic effects: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/ kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus. **Nursing Mothers:** Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother. **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 2 years have not been established. **Geriatric Use:** No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY: Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an in vitro bacterial reverse mutation (Ames) test, an in vitro mammalian chromosome aberration assay or an in vivo mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

U.S. Patents Nos. 5,641,805; 6,995,186; 7,402,609

References: 1. IMS Health, IMS National Prescription Audit™, August 2010 to September 2012, USC 61500 OPHTH ANTI-ALLERGY. **2.** Blaiss MS, Tort MJ. Zero itch in eyes treated with olopatadine hydrochloride ophthalmic solution, 0.2% in bilateral conjunctival allergen challenge studies. Poster presented at: World Allergy Conference; December 2011; Cancun, Mexico.

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Treating Glaucoma: In Defense of ECP

Endoscopic cyclophotocoagulation is less widely used than many other procedures, but has some strong points in its favor.

Diamond Y. Tam, MD, Toronto

Of all the tools in a glaucoma surgeon's armamentarium, endoscopic cylcophotocoagulation—in which fiber optics allow the surgeon to partially coagulate ciliary process tissue from inside the eye, reducing the production of aqueous—may be one of the least often used. I suspect that most surgeons think of it as the final option in the toolbox: When everything else has failed, you resort to ECP to try to save the eye from a really high pressure that you haven't been able to control with a tube or trabeculectomy. In addition, my impression is that in most places, when a patient needs an ECP for refractory glaucoma, the doctor usually sends him to a vitreoretinal surgeon who goes in via the pars plana to do the procedure.

I began performing ECP in 2004 when I trained at the University of California San Francisco. In 2007 I did my fellowship with Ike Ahmed, MD, who introduced me to the concept of endoscopic cycloplasty (more on that in a minute). I've been performing ECP ever since, and I've found it to be a very useful tool for many patients with glaucoma or ocular hypertension.

Here, I'd like to explain how I use ECP and why I believe many more patients could be benefiting from it.

The Advantages of ECP

ECP is a bit of a unique animal, in that almost all other combined cataract/glaucoma procedures are mainly aimed at increasing the outflow of aqueous. ECP acts by reducing the creation of aqueous—turning down the tap a little bit, so to speak.

One of the strongest points in favor of ECP is its low-risk profile. Previously, the comparison would have been to tubes or trabeculectomies, which of course have a much higher risk profile. With trabeculectomy, for example, you have a lifetime risk of infections, bleb failure and other potentially visually devastating complications. Today, however, the landscape of glaucoma surgery is changing with the advent of microinvasive glaucoma surgery devices like the iStent or Trabectome, which are making glaucoma surgery a lot safer. But even compared to these options, I see ECP as being on the low end of the risk spectrum. Devices, while overall fairly safe, have the potential to dislocate inside the eye, and they are foreign bodies that may incite inflammatory responses or result in hyphema or angle bleeding. Furthermore, those procedures are more technically challenging than ECP is to perform. So, I still believe that ECP is one of the lowest-risk options available.

As noted, ECP is also relatively easy to perform. As an addendum to cataract surgery it's low in invasiveness, and it doesn't add more than a few minutes to the procedure—a small price to pay for buying patients the opportunity to delay or possibly forego filtration surgery down the road. It may also help preserve patients' vision; if you can get them to a lower pressure earlier, they may avoid disc damage they would eventually have had 20 or 30 years later.

Another advantage of the ECP procedure is that the visualization of the ciliary body via the fiber optic viewer occasionally reveals problems that were otherwise invisible to the surgeon. We've treated some patients who had very narrow angles and

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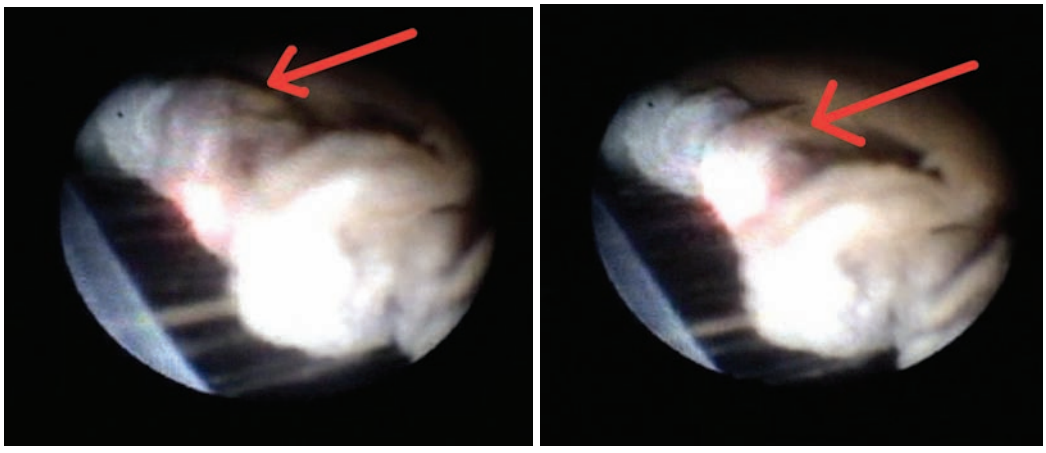

Above left: The red arrow indicates a "high-riding" ciliary process before ECP treatment. Right: The same ciliary body process has shrunken down one second after treatment.

discovered large cysts in the ciliary body or iris. Sometimes these can be seen preoperatively on gonioscopy or via ultrasound biomicroscopy, but not always. That discovery can give you a window into the reason for certain pathologies.

ECP is also titratable; it allows the surgeon to adjust the size of the arc being targeted with the laser based on the patient's status. I usually "paint" about 270 degrees, just because that's the approximate arc I can comfortably reach through a single temporal incision. But if a patient has refractory glaucoma you can easily make a second incision allowing you to cover 360 degrees. (On the other hand, if you need that much ablation you may be looking at advanced glaucoma that might be better addressed with a different procedure.)

ECP: Opening Narrow Angles

Perhaps the most useful role for ECP in cataract surgery when glaucoma is a concern is in patients who have narrow angles. Most surgeons think of ECP as a means to reduce IOP by decreasing aqueous production, and it certainly is useful in that capacity. However, ECP also allows us to manipulate the position and size of the ciliary body and processes. That means we can open up the angle in patients who have narrow angles at the time of cataract surgery. My colleague Dr. Ahmed coined the term "endoscopic cycloplasty" (abbreviated ECPL) to describe this use of ECP.

The technique is fairly straightforward. Wherever the laser strikes, the tissue is coagulated, and the remaining tissue shrinks towards the coagulated area. So in a narrow-angle patient, you aim the laser at the posterior end of the process. After you fire the laser, the process shrinks downward, opening the angle. *(See images, p. 82.)* Obviously, you would not want to start at the top of the process, which would have the opposite effect.

I've seen some very dramatic examples of this treatment's effectiveness in patients whose angles were almost appositional; you could hardly see the trabecular meshwork at all before surgery. After surgery with ECP, the angle is typically wide open, Shaffer grade 4. This is especially useful in patients who have plateau iris, where the ciliary processes are riding very high up. (Cataract surgery by itself may help these patients a little, but some patients with plateau iris can still end up with very narrow angles.)

Depending on your intention, you can focus primarily on opening the angle or reducing aqueous production, or both. In narrow-angle eyes, our usual focus is mainly on opening the angle. However, we'll occasionally have a very narrow angle patient who has pressure in the mid-20s but no visual field damage—preperimetric glaucoma or possibly ocular hypertension. In those cases I use ECP to shrink the ciliary process backwards first and then paint the entire process to reduce the intraocular pressure as well. On the other hand, if the angle was very narrow but the patient's preop pressure was 13 mmHg on no meds, I'd primarily treat to open the angle. We can do as much of either approach as we feel is necessary.

Of course, patients sometimes have combined- or mixed-mechanism glaucoma, where they do have narrow angles, but that alone isn't sufficient to account for the amount of disc disease or visual field loss. For example, a patient may have grade-2 angles with no visible synechiae or evidence of intermittent or chronic angle closure, yet he has a large field defect or a notch on the nerve and his pressure is in the mid-20s. Clearly, this patient also has some trabecular meshwork dysfunction. Of course, you can still use ECP in those cases, but I'm a little less optimistic that ECP alone will get those patients to your target pressure, depending on what pressure you're aiming for.

Addressing Surgeon Reluctance

Given the usefulness of the

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The concern for the devastating shortfall in eye care education in developing communities, especially for correction of refractive error, became action in 1998 for those at the Institute. The lack of training institutes and educational opportunities was creating a human resource gap and a critical eye care shortage for hundreds of millions of people in need of services. The concern and willingness to address the issue gave rise to the International Centre for Eyecare Education (ICEE).

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The Durban community in South Africa, arrives in hundreds to support the Brien Holden Vision Institute's initiative Drive for Sight, part of the World Sight Day celebrations in October 2012. All attendees were offered free eye examinations, access to free or affordable low cost spectacles and referrals for further eye care where necessary. ***Photo by Graeme Wyllie.***

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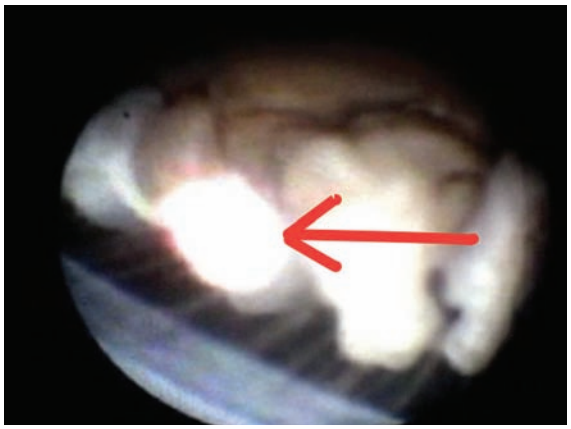

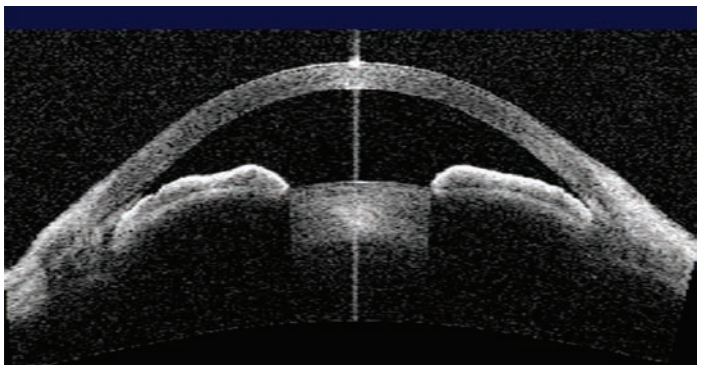

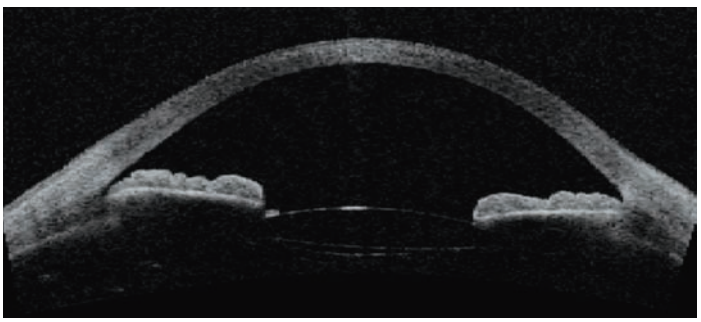

ECP can also be used to open narrow angles, a process referred to as "endoscopic cycloplasty" or ECPL. Wherever the laser strikes, the tissue is coagulated and the remaining tissue shrinks towards the coagulated area. So in a narrow-angle patient, firing the laser at the posterior end of the process (above) causes the process to shrink downward, opening the angle, as in the sample case shown to the right.

procedure, why are so many surgeons reluctant to use it? Part of the reason may be a fear of hypotony, which many surgeons associate with cycloablation procedures. This is ironic, because I've performed ECP for nine years, and I have yet to see a patient—cataract or otherwise—who had hypotony issues afterward. In contrast, I've seen a number of cases where we did cataract surgery with a tube shunt or trabeculectomy and the patient had hypotony for weeks while we waited for the pressure to increase a little bit.

One reason that ECP doesn't lead to hypotony is that there appears to be little danger of destroying all of the aqueous-producing epithelium, even if you treat 360 degrees. The ciliary body has a large surface area because of all the nooks and crannies and the cracks between each ciliary process. In the usual ECP treatment, the laser simply doesn't treat all of the tissue in the area at which it's aimed.

The fear that ECP will lead to hypotony may be the result of people automatically thinking of transscleral cyclophotocoagulation, which produces an entirely different degree of tissue destruction from ECP. With TCP, where the laser is targeted from outside the eye, the energy can affect a much broader tissue area. Many histological studies have demonstrated that while TCP can do massive damage, ECP doesn't destroy underlying tissue structure. TCP is a much more invasive process, and—unlike ECP—definitely brings with it a risk of hypotony.

Unfortunately, it only takes one case producing unwanted results to cause a surgeon to avoid a procedure. I've noted, for example, that a lot of surgeons who routinely use intracameral antibiotics have experienced a case of endophthalmitis that didn't go well. Similarly, I think that when people have seen tissue destruction or hypotony from TCP, they become afraid to resort to cycloablation, even though those concerns do not directly apply to ECP.

Another likely reason for less-frequent use of ECP is the cost of the instrument. To many surgeons, it's a tool of last resort. And although it's especially helpful for treating patients with narrow angles, practice demographics may limit the number of patients you see who have narrow angles. If you believe you'll only use it once a year, it's understandable that you might hesitate to spend the money to purchase the instrument.

When ECP Isn't Ideal

One of ECP's limitations is its inability to produce a very low target pressure. Typically, ECP only produces a pressure in the mid-teens (a criticism often leveled at other minimally invasive glaucoma procedures as well). That's because of episcleral venous pressure, which limits how low you can get the pressure using these approaches. Of course, this also is the argument as to why these procedures are safer; the risk of hypotony with a Schlemm's canal device is extremely low, and the same is true for ECP.

Nevertheless, if your target pressure is very low, ECP is probably not your procedure of choice. If a patient has a severe hemifield cut and you want his pressure to be 10 mmHg, you

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probably would want to use a different treatment. On the other hand, if the patient has a very early arcuate scotoma and very mild mean deviation and your target pressure is in the mid-teens, I'd say ECP would be an excellent option to choose.

Another thing we've noted, although we don't have clinical data to support this yet, is that ECP is not very efficacious in pseudoexfoliation patients. Even when we do the ECP intraoperatively, the ciliary processes don't seem to take up the laser energy as well. We can't say for certain what the reason is, but if you look at the processes with an endoscope during surgery, you can see the pseudoexfoliation material covering the zonules, and the ciliary processes look more white. So it could be a matter of less pigment being present, or possibly the result of the dandruff-like pseudoexfoliation material blocking the uptake of the laser. You typically have to turn the laser power up higher with these patients, and even so, the processes don't seem to respond quite as dramatically during surgery.

This is not to say that a patient with pseudoexfoliation isn't a candidate for ECP. I would still try ECP as a first-line therapy if the patient had pseudoexfoliation but has a narrow angle and a mild degree of glaucoma. In that situation, ECP might indeed help to open the angle and get the patient to a lower pressure, allowing him to avoid a more invasive procedure like a trabeculectomy down the road.

I also don't use ECP in patients who have a history of uveitis or uveitic glaucoma, primarily for two reasons. First, ECP will stir up more inflammation postoperatively—at least in the early postop period—and in these patients, minimal inflammation is desirable. Many of them will have difficulty getting their uveitis controlled even if cataract surgery is performed without ECP. Second, although uveitic patients can have a high intraocular pressure, they are also prone to hyposecretion where the ciliary body can shut down and produce very little aqueous, leading to hypotony.

An Option with Promise

Despite its lack of widespread use, ECP has potential as a tool for addressing certain types of glaucoma—in particular, glaucoma attributable to a narrow angle. Given the difficulty and importance of addressing this disease, I think it's a tool more surgeons should consider adding to their armamentariums. REVIEW

Dr. Tam is in private practice in the Toronto area. He has no financial interest in any of the technologies discussed above.

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A range of instruments and hand-pieces made from lightweight and durable titanium in several gauges are also available, including Retilock, a one-step self-retaining trocar system for easy access to the posterior segment.

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- disposable PFCL and subretinal cannulas;
- scleral buckling components;
- vitrectomy lenses; and
- Invitria, Intravitreal Injection Assistant.

FCI says it's performed extensive research and development to provide surgeons with outstanding products that enhance the efficiency and effectiveness of vitreoretinal procedures. For information, call 1 (800) 932-4202, fax (781) 826-9062, or e-mail info@fci-ophthalmics.com.

This article has no commercial sponsorship.

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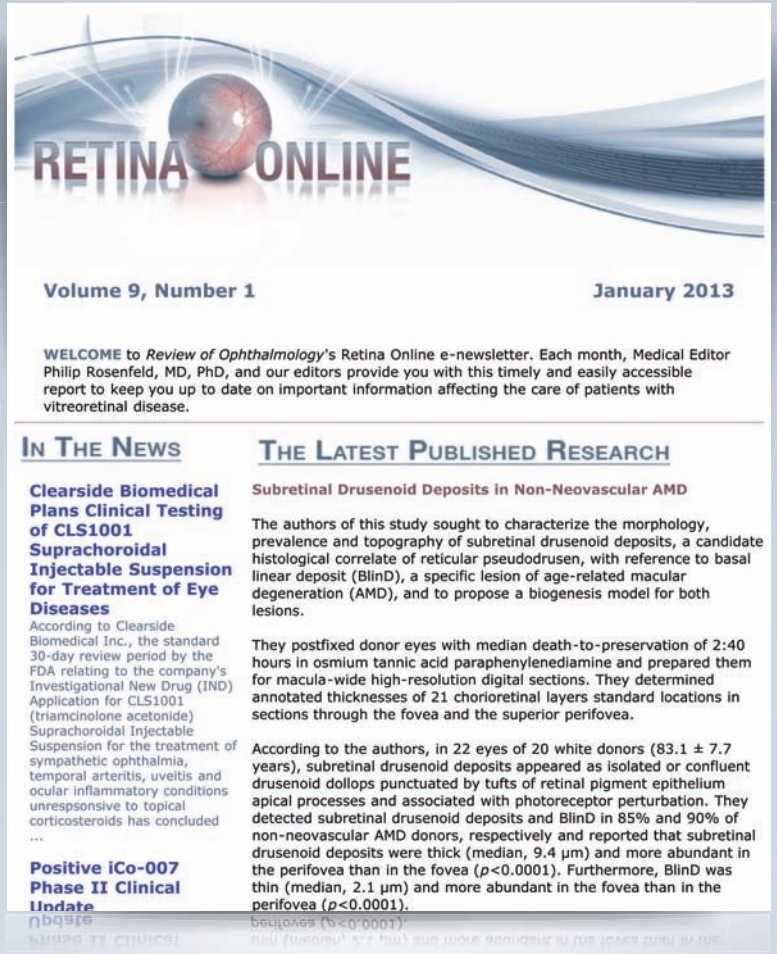

RETINA ONLINE

Volume 9, Number 1 January 2013

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

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

Positive iCo-007 Phase II Clinical Update

THE LATEST PUBLISHED RESEARCH

Subretinal Drusenoid Deposits in Non-Neovascular AMD

The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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Alcon Launches Ilevro Suspension Post-Cataract Drop

Alcon announced the launch of Ilevro Suspension, a new once-daily treatment option for pain and inflammation associated with cataract surgery. In two double-masked, randomized clinical trials, Ilevro Suspension demonstrated superior clinical efficacy compared to its vehicle.

In the studies, patients treated with Ilevro Suspension were less likely to have ocular pain and measurable signs of inflammation (cells and flare) at the end of treatment than those treated with its vehicle.

Patients administered Ilevro Suspension experienced superior outcomes when compared to those on vehicle in the following areas:

- Inflammation resolved at day 14 in 65 percent of Ilevro Suspension patients vs. 32 percent of patients on vehicle.
- Pain resolution rates in Ilevro Suspension-treated patients were 86 percent compared to 46 percent of patients on vehicle.

The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure and sticky sensation. These reactions occurred in approximately 5 to 10 percent of patients. For more information, visit alcon.com.

Accutome A-Scan Plus for Fast Axial Length Capture

Accutome has introduced the A-Scan Plus Connect, providing critical ophthalmic measurements for cataract surgery that is compatible on laptop, PC or tablet platforms. The compact tool eases the work measuring and calculating patients' axial length for cataract surgery.

Accutome says its A-Scan Plus Connect captures axial length faster than typical A-scans and with an industry-leading resolution. The recently FDA-approved product also features an improved and easy-to-upgrade software interface and calculation menus. The A-Scan Plus Connect's direct-connect ability allows for an easy transfer of electronic medical records. It is laptop-based compared to most A-Scan devices, which are stand-alone. Its portable and lightweight structure further allows for effortless maneuvering from office to office.

For information, visit accutome.com, e-mail info@accutome.com or call 1(800) 979-2020.

Volk Debuts New Lens Sets for Diagnostic and Laser Work

Volk Optical has released several Best in Class lens sets, packaging together complementary lenses for simple selection and better value. Two sets are available for its Digital non-contact lens series and one set for high-resolution contact imaging.

Volk's Digital Series lenses provide the highest resolution for non-contact imaging during both BIO and slit-lamp use. The Digital family's lenses increase general diagnostic capabilities and shorten exam time, says Volk. The two-lens set includes Volk's Digital Wide Field, a 90-D power lens with a field of view 40 percent larger than that of a classic 90-D, and the Digital High Mag, for true three-dimensional views of the posterior pole—an upgrade to a classic 78-D lens. The three-lens set adds the Digital Clear Field. A

(Continued on page 97)

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The vision to help you succeed

Before reading on, please see p. 98 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

A complete peripheral retinal exam was conducted of both eyes, and revealed a yellow-red mass with extensive exudate inferotemporally in the right eye *(See Figure 3)*. The mass was fed by a minimally dilated retinal artery and drained by a slightly dilated vein. At this point, the differential diagnosis included retinal vasoproliferative tumor and retinal hemangioblastoma. B-scan ultrasonography revealed an acoustically dense mass but did not help to narrow the differential diagnosis. A fluorescein angiogram was not performed. Given the moderately older patient age and lack of medical history, as well as the unifocality of the vascular mass and its lack of substantial vascular feeder vessels, the diagnosis of retinal vasoproliferative tumor appeared more favorable. Retinal hemangioblastoma and von Hippel-Lindau disease were felt to be less likely. The patient was treated with cryotherapy and sub-Tenon's fascia triamcinolone (40 mg/cc) injection. At four months post-treatment, the retinal tumor showed early regression and the ERM was less prominent, with reduced macular edema and relatively stable visual acuity at 20/40. At 10 months post-treatment, the tumor was completely regressed and the ERM had retracted up to the optic disc with resolution of the retinal edema *(See Figure 4)*. At this point, vision improved to 20/25, and it has remained stable since.

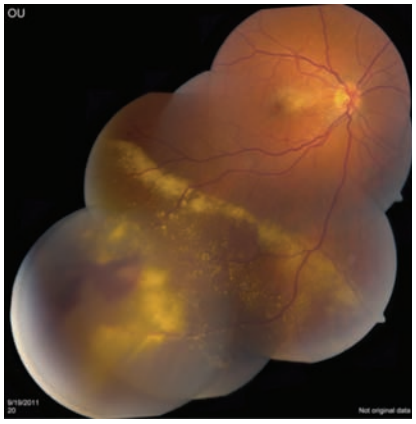

Figure 3. Fundus photograph of right eye demonstrating a yellow-red peripheral mass with extensive subretinal and intraretinal exudate.

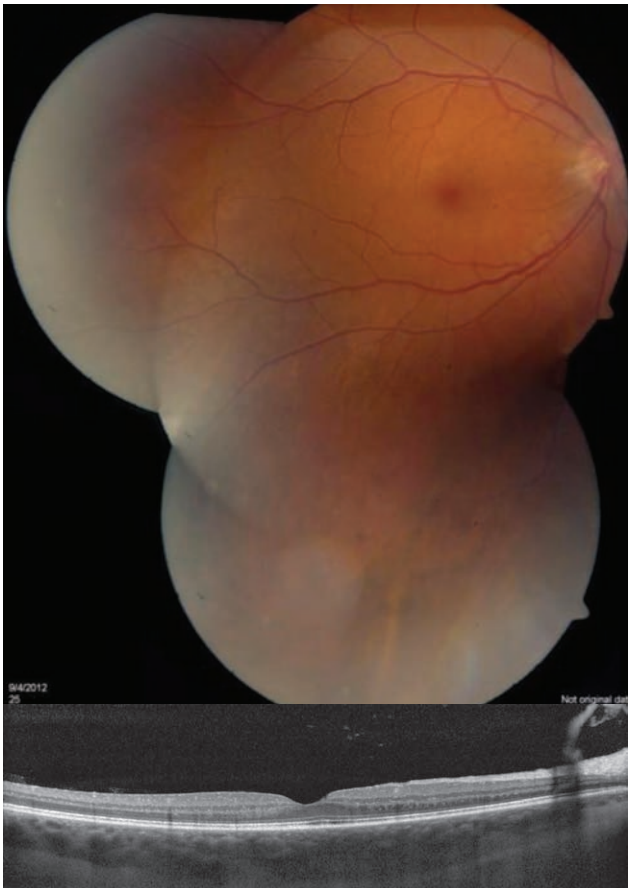

Figure 4. Top: Ten months post-cryotherapy right eye. Fundus photograph showing residual ERM that has scrolled up over the optic disc, and resolution of retinal striae. OCT confirms these findings and shows resolution of cystoid macular edema.

Discussion

Vasoproliferative tumor (VPT) is a vascular tumor that appears as a yellow-red peripheral retinal mass, often with related visual loss from macular edema or ERM.[1] Carol Shields, MD, and Jerry Shields, MD, and colleagues initially reported a series of 12 tumors in an early 1983 paper,[2] then later clarified the clinical features and management in 129 cases.[1] Most recently they published a comparative update describing 334 vasoproliferative tumors in 275 patients.[3] The latest publication is a comparison of the features of primary versus secondary VPT features.

The typical VPT is associated with extensive subretinal and intraretinal exudation, located in the peripheral inferotemporal quadrant (67 percent). It appears acoustically dense on ultrasonography and hyperfluorescent in arterial

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LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis: 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.

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

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

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric Use: Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs: Patients should be advised that if more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

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and venous phases on fluorescein angiography. In their cohort of 295 eyes, Drs. Shields and colleagues identified an associated ocular condition in 20 percent of patients, and categorized these as secondary VPT. The most common cause of secondary VPT was retinitis pigmentosa (22 percent); pars planitis (21 percent); Coats' disease (16 percent); retinal detachment post-repair (13 percent); and idiopathic retinal vasculitis (6 percent). Patients with secondary VPT were younger and more symptomatic than those with primary VPT.[3] Eyes with secondary VPT were significantly more likely to be bilateral, multifocal and posterior to the equator.[3] The average time between diagnosis of the primary process and the VPT was 160 months.

Pathologic studies of VPT have been limited, given the rare need for enucleation or biopsy, but have consistently shown the mass to be made up of spindle-shaped cells that stain strongly positive for glial fibrillary acidic protein, which suggests a fibrocytic astrocyte cellular origin.[4,5] Abnormal vascular channels with hyalinized walls are seen within the spindle cell mass. In a recent study of four cases, Lynn Janet Poole Perry, MD, and colleagues performed an array of immunohistochemical stains that showed a somewhat surprising paucity of microvascular channels despite the apparent vascularity of this tumor clinically.[4] When combined with their findings of low cellular turnover and lack of markers seen in astrocytic neoplasms, the authors postulated that VPT are primarily a reactive astrocytosis associated with fibrous retinal pigment epithelial metaplasia and subretinal exudate. Marianne Smeets and colleagues likewise favor a reactive process involving both glial and vascular cells.[5]

In the Shields' series, visual complaints were largely related to macular edema (24 percent), macular ERM (20 percent), macular exudate (23 percent) and vitreous hemorrhage (19 percent).[3] In our case, the patient presented with mildly decreased vision secondary to macular ERM with macular edema. A wide range of retinal pathology has been implicated in ERM formation, including retinal vascular disease; inflammatory disease; post-traumatic/postoperative; retinal break; and intraocular tumors (particularly vascular tumors).[6]

Treatment options for VPT include observation for asymptomatic non-leaking tumors, but if there is related visual loss, subretinal fluid or exudation, then laser photocoagulation, cryotherapy, photodynamic therapy or plaque radiotherapy are considered. While no clear treatment protocol exists, our preferred treatment modality for most patients with symptomatic VPT is cryotherapy.

This case highlights the importance of a detailed peripheral retinal examination in all cases of ERM, looking for retinal breaks, inflammation and peripheral masses. The treatment of VPT is based on the individual patient's symptoms. Observation, cryotherapy and laser photocoagulation are currently the primary treatment options. REVIEW

The authors would like to thank Carol Shields, MD, and Jerry Shields, MD, of the Ocular Oncology Service at Wills Eye Institute for their invaluable assistance in preparing this case report.

1. Shields CL, Shields JA, Barrett J, De Potter P. Vasoproliferative tumors of the ocular fundus: Classification and clinical manifestations in 103 patients. Arch Ophthalmol 1995;113:615-23.
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3. Shields CL, Kaliki S, Al-Daamash S, Shukla S, et al. Retinal vasoproliferative tumors. Comparative clinical features of primary versus secondary tumors in 334 cases. JAMA Ophthalmol 2013; in press.
4. Poole Perry LJ, Jakobiec FA, Zakka FR, Reichel E, Herwig MC, Perry A, Brat DJ, Grossniklaus HE. Reactive retinal astrocytic tumors (so-called vasoproliferative tumors): Histopathologic, immunohistochemical, and genetic studies of four cases. Am J Ophthalmol Pub Online Dec. 6, 2012.
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(Continued from page 89)

hybrid of a 20-D and 28-D lens, with magnification of a 20-D and field of view of a 28-D, the Digital Clear Field offers the best of both lenses.

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For more information, visit haag-streit-usa.com. REVIEW

A patient suspects her blurred vision is related to seasonal allergies and seeks a diagnosis at Wills Eye Institute.

Joshua R. Ehrlich, MD, MPH, and Brian C. Doyle, MD

Presentation

A 44-year-old Caucasian female presented to Wills Eye complaining of blurred vision in the right eye with mild worsening of vision over the past four months. She believed that her symptoms were related to seasonal allergies. She denied pain, diplopia, field loss, metamorphopsia, flashes or floaters.

Medical History

The patient denied any prior ocular or significant systemic medical history, and took no medications. She noted a family history of prostate, bladder, lung and pancreatic cancer.

Examination

Ocular examination revealed visual acuity in the right eye without correction of 20/30+2 without pinhole improvement and 20/20 in the left eye. Pupils were reactive without a relative afferent pupillary defect. Ocular motility in both eyes was full and there were no visual field defects on confrontational testing. Applanation tonometry measured an intraocular pressure of 18 mmHg in the right eye and 17 mmHg in the left eye.

Slit-lamp examination revealed an unremarkable external, adnexal and anterior segment in both eyes. Exam of the posterior pole of the right eye was remarkable for an epiretinal membrane with retinal striae, macular edema and early neovascularization of the optic disc *(See Figure 1)*. Posterior exam of the left eye was unremarkable. Optical coherence tomography was performed, showing the ERM with cystoid macular edema in the right eye, and a normal left eye *(See Figure 2)*.

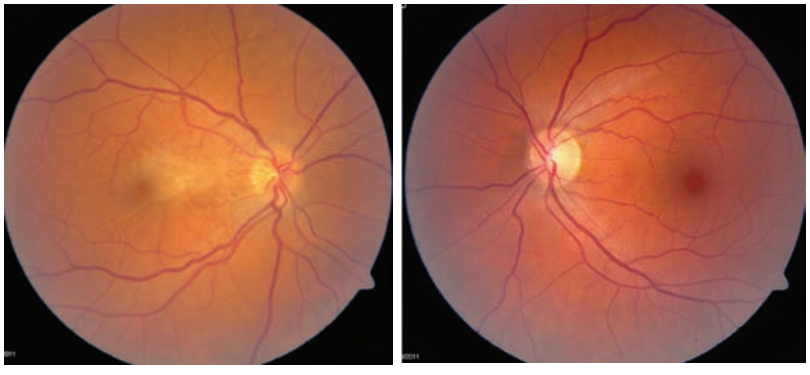

Figure 1. Left: Fundus photograph of right eye showing epiretinal membrane with retinal striae and optic disc neovascularization. Normal left eye fundus photo.

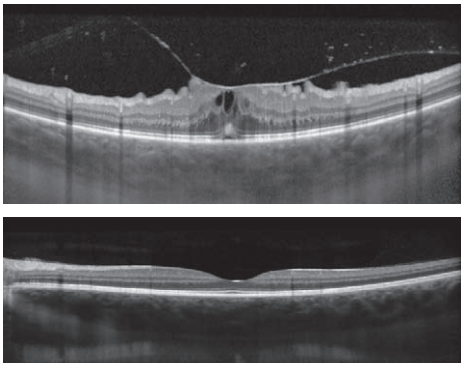

Figure 2. Top: Optical coherence tomography of right eye demonstrating epiretinal membrane with cystoid macular edema. Below: A normal OCT of left eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 96

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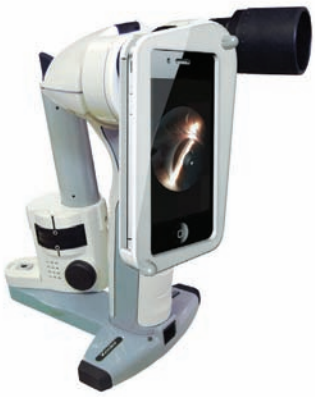

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Indication: LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Important Safety Information

Warnings and Precautions: LUMIGAN® causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN®. LUMIGAN® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

Please see Brief Summary of the full Prescribing Information on adjacent page.

Write it RIGHT 0.01%

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%