REVIEW® of Ophthalmology

January 2015

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IOL ISSUE

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NEW SERIES:
MASTERS OF SURGERY P. 44

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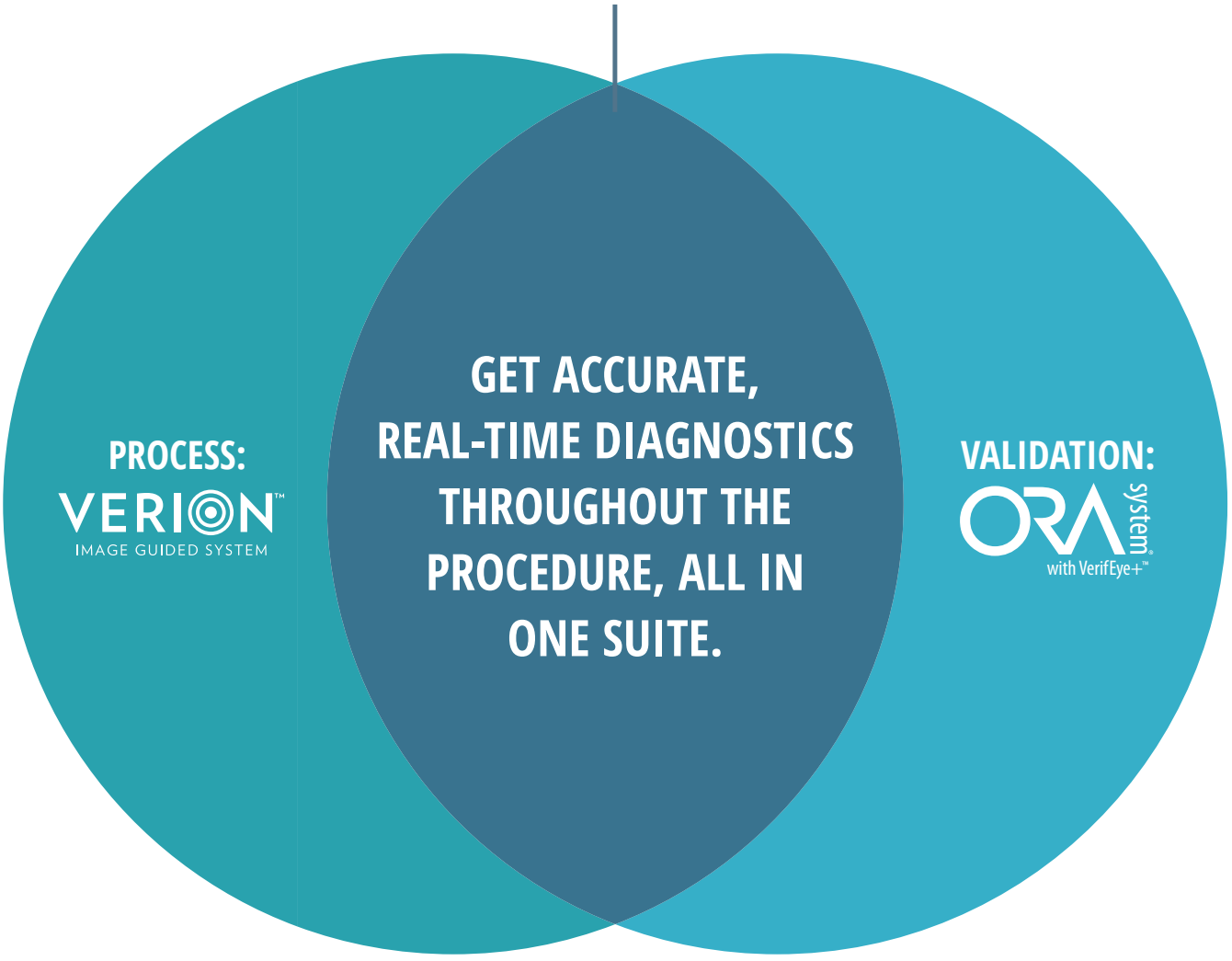

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† Intended target is defined as within 0.5 D of targeted astigmatism.
1. Alcon data on file.

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THE CATARACT REFRACTIVE SUITE BY ALCON

VERION™ REFERENCE UNIT AND VERION™ DIGITAL MARKER IMPORTANT PRODUCT INFORMATION

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

INTENDED USES: The VERION™ Reference Unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a patient's eye in order to determine the radii and corneal curvature of steep and flat axes, limbal position and diameter, pupil position and diameter, and corneal reflex position. In addition, the VERION™ Reference Unit provides preoperative surgical planning functions that utilize the reference image and preoperative measurements to assist with planning cataract surgical procedures, including the number and location of incisions and the appropriate intraocular lens using existing formulas. The VERION™ Reference Unit also supports the export of the high-resolution reference image, preoperative measurement data, and surgical plans for use with the VERION™ Digital Marker and other compatible devices through the use of a USB memory stick. The VERION™ Digital Marker links to compatible surgical microscopes to display concurrently the reference and microscope images, allowing the surgeon to account for lateral and rotational eye movements. In addition, the planned capsulorhexis position and radius, IOL positioning, and implantation axis from the VERION™ Reference Unit surgical plan can be overlaid on a computer screen or the physician's microscope view.

CONTRAINDICATIONS: The following conditions may affect the accuracy of surgical plans prepared with the VERION™ Reference Unit: a pseudophakic eye, eye fixation problems, a non-intact cornea, or an irregular cornea. In addition, patients should refrain from wearing contact lenses during the reference measurement as this may interfere with the accuracy of the measurements. Only trained personnel familiar with the process of IOL power calculation and astigmatism correction planning should use the VERION™ Reference Unit. Poor quality or inadequate biometer measurements will affect the accuracy of surgical plans prepared with the VERION™ Reference Unit. The following contraindications may affect the proper functioning of the VERION™ Digital Marker: changes in a patient's eye between preoperative measurement and surgery, an irregular elliptic limbus (e.g., due to eye fixation during surgery, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgery should be avoided.

WARNINGS: Only properly trained personnel should operate the VERION™ Reference Unit and VERION™ Digital Marker. Only use the provided medical power supplies and data communication cable. The power supplies for the VERION™ Reference Unit and the VERION™ Digital Marker must be uninterruptible. Do not use these devices in combination with an extension cord. Do not cover any of the component devices while turned on. Only use a VERION™ USB stick to transfer data. The VERION™ USB stick should only be connected to the VERION™ Reference Unit, the VERION™ Digital Marker, and other compatible devices. Do not disconnect the VERION™ USB stick from the VERION™ Reference Unit during shutdown of the system. The VERION™ Reference Unit uses infrared light. Unless necessary, medical personnel and patients should avoid direct eye exposure to the emitted or reflected beam.

PRECAUTIONS: To ensure the accuracy of VERION™ Reference Unit measurements, device calibration and the reference measurement should be conducted in dimmed ambient light conditions. Only use the VERION™ Digital Marker in conjunction with compatible surgical microscopes.

ATTENTION: Refer to the user manuals for the VERION™ Reference Unit and the VERION™ Digital Marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

ORA™ SYSTEM IMPORTANT PRODUCT INFORMATION

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

INTENDED USE: The ORA™ System uses wavefront aberrometry data in the measurement and analysis of the refractive power of the eye (i.e. sphere, cylinder, and axis measurements) to support cataract surgical procedures. **CONTRAINDICATIONS:** The ORA™ System is contraindicated for patients:

- who have progressive retinal pathology such as diabetic retinopathy, macular degeneration, or any other pathology that the physician deems would interfere with patient fixation;
- who have corneal pathology such as Fuchs', EBMD, keratoconus, advanced pterygiumim pairing the cornea, or any other pathology that the physician deems would interfere with the measurement process;
- whose preoperative regimen includes residual viscous substances left on the corneal surface such as lidocaine gel or viscoelastics;
- with visually significant media opacity (such as prominent floaters or asteroid hyalosis) what will either limit or prohibit the measurement process; or
- who have received retro or peribulbar block or any other treatment that impairs their ability to visualize the fixation light.

In addition, utilization of iris hooks during an ORA™ System image capture is contraindicated, because the use of iris hooks will yield inaccurate measurements.

WARNINGS AND PRECAUTIONS:

- Significant central corneal irregularities resulting in higher order aberrations might yield inaccurate refractive measurements.
- Post refractive keratectomy eyes might yield inaccurate refractive measurement.
- The safety and effectiveness of using the data from the ORA™ System have not been established for determining treatments involving higher order aberrations of the eye such as coma and spherical aberrations.
- The ORA™ System is intended for use by qualified health personnel only.
- Improper use of this device may result in exposure to dangerous voltage or hazardous laser-like radiation exposure.
- Do not operate the ORA™ System in the presence of flammable anesthetics or volatile solvents such as alcohol or benzene, or in locations that present an explosion hazard.

ATTENTION: Refer to the ORA™ System Operator's Manual for a complete description of proper use and maintenance of the ORA™ System, as well as a complete list of contraindications, warnings and precautions.

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REVIEW® of Ophthalmology

ENRICH YOUR PRACTICE

Review of Ophthalmology delivers current and comprehensive information focusing on topics such as disease diagnosis, surgical techniques and new technologies.

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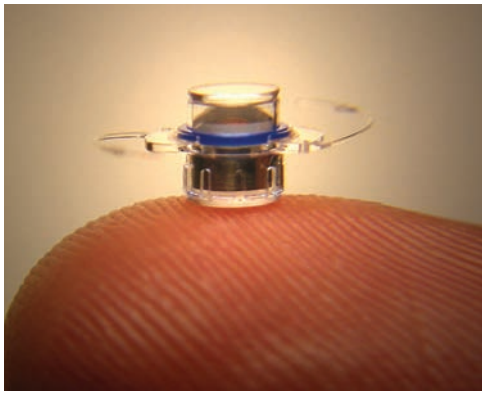
REVIEW NEWS
Volume XXII • No. 1 • January 2015

Indication Expanded for End-Stage AMD Scope

In the fall of 2014, VisionCare Ophthalmic Technologies, maker of the Implantable Miniature Telescope intraocular lens for end-stage age-related macular degeneration patients, was granted an expanded indication that lowered the minimum age for implantation to 65. Around the same time, the Centers for Medicare & Medicaid Services allowed reimbursement when the device is implanted at an ambulatory surgery center. Both developments may expand the adoption rate of the technology.

The IMT is a lens system 3.6 mm wide and 4.4 mm long that's implanted in the capsular bag through a large incision. Once inside the eye, it uses wide-angle micro-optics that, when combined with the cornea's optics, create a telephoto system that magnifies objects in front of the eye by approximately 2.2 to 2.7 times. In the end-stage AMD patient with a central macular blind spot, this magnification takes central images and projects them onto healthy areas of the retina. In a long-term study of the device, 103 (59.5 percent) of 173 telescope-implanted eyes gained three or more lines of best-corrected vision, compared to 18 (10.3 percent) of 174 fellow control eyes.[1] In the Food and Drug Administration trial of the IMT, the mean best-corrected distance vision went from 20/312 to 20/171 at four years.



Thanks to a new FDA ruling, patients 65 years of age with end-stage AMD can now receive the Implantable Miniature Telescope.

"Decreasing the minimum age to 65 will expand the number of patients eligible for the treatment," says Los Angeles retinal specialist David Boyer, who evaluates patients for possible IMT implantation. "We have a paper due to come out that shows younger patients do better than even the older patients. This would allow patients with visual loss secondary to AMD to avail themselves of this treatment earlier."

Memphis, Tenn., retinal specialist Steve Charles, also a clinical professor at the University of Tennessee, says that though the IMT gives some visual improvement to patients, it has limitations. "First and foremost, it gives a very modest visual improvement," Dr. Charles says. "We're not dealing with a patient who is 20/400 becoming able to read small print. Also, because of the reduced field of view, a patient can't drive with this. It also results in marked aniseikonia—the image size is different between the two eyes—which poses a falling risk. In addition, today we have very viable, successful treatments for AMD such as Eylea and Lucentis, which may mean patients' vision doesn't reach the point where they're eligible for the IMT. Finally, implantation requires a very large incision at a time when the cataract community is striving for smaller ones."

Dr. Boyer acknowledges that patients have to be properly screened to be able to handle the new vision from the IMT. "Not everyone with geographic atrophy or end-stage wet AMD is eligible for it," he says. "A lot of patients can't tolerate it and feel off-balance. It requires some training, and part of [VisionCare's] CentraSight program is to ensure that patients are well-screened so that patients who will benefit the most will have it. These aren't driving patients. There are some patients with external telescopes that do drive, because they have a bioptic or something that enables them to do that. I wouldn't put the IMT in those driving patients because they'd probably lose the ability to drive, and would need the peripheral vision in the other eye and different clues to be able to drive.

"It's true that we're able to reduce vision loss tremendously [with anti-VEGF treatments]," Dr. Boyer continues. "But, if you follow these patients longer, even some on treatment will lose vision if they develop dry AMD changes."

VisionCare has initiated a patient education and support program about end-stage AMD and the IMT called

CentraSight. Through the program, patients can see if they meet eligibility criteria and experience a simulation of what vision would be like with the IMT. Dr. Boyer notes that, again, not everyone will qualify. "I think a patient who is doing well with his low-vision aids would probably not be a candidate, or someone for whom I'd recommend this treatment," he says. "However, there are patients who say, 'I get some improvement with a telescope mounted externally,' and, if they qualified in every other way, they might be happy, because the vision quality that results from putting the lens inside the eye may be much greater for them."

1. Hudson HL, Stulting RD, Heier JS, Lane SS, et al, IMT002 Study Group. Implantable telescope for end-stage age-related macular degeneration: Long-term visual acuity and safety outcomes. Am J Ophthalmol 2008;146:5:664-673.

Allergan/Actavis Turn Sights to the Task of Merging

Following months of fending off a hostile takeover, Allergan is moving forward as part of Dublin, Ireland-based Actavis; the combined company is now ranked as one of the top 10 global pharmaceutical companies by sales revenue.

Brent Saunders, CEO and president of Actavis, said the genesis of the Allergan acquisition lay in the fundamentals. "Allergan is one of the best-managed, best companies in our sector," he said. "It holds a leadership position in all of the therapeutic areas it competes in and has a great commitment to the health-care pro-

Actavis CEO Brent Saunders

fessionals it serves. It has a best-in-class pipeline of innovation and commitment to R&D."

Formerly the CEO of Bausch + Lomb, Mr. Saunders knows ophthalmology well and recognizes the profession's unique relationship with industry. "You really have an engaged physician audience," he said. "Ophthalmologists appreciate innovation; they like to understand the science and technology behind innovation. They're very open to advancing eye health and looking for ways to solve unmet medical needs in partnership with industry. That's a really nice collaboration to have with your physicians."

Of the struggle to keep control of the company throughout most of 2014, Allergan CEO David Pyott said, "If there is an irony in all of this, it's that we will have the best sales-growth year in our 64-year history. Year-to-date, sales have grown 16 percent across the board. Within ophthalmology, we have been the fastest-growing fully integrated ophthalmic company globally, with IMS showing about 14 percent growth in ophthalmics."

"Fortunately, Brent and I have known each other for a while," said Mr. Pyott. "He had indicated his interest at a very high level a couple of months ago. And that led to conversations. We came together because we realized the two companies have a lot of common goals. We believe in innovation. Actavis this year, as a company on its own, is spending about $1.3 billion on R&D. To their credit, they have been successful. They have no fewer than seven new drug applications at the FDA. That's a testament to the fact that not only do they spend, but they're very successful. We too have been successful. I think we're now up to 14 products approved by the FDA since 2010."

The two leaders see the ophthalmology component of Allergan surviving intact. "In terms of the future operations, because there is really no overlap in ophthalmology per se, Actavis will leave a successful team in place" at Allergan, said Mr. Pyott.


Allergan CEO David Pyott

Bloomberg News reported in late December that much of the leadership at Allergan will be assumed by Actavis executives. Mr. Pyott was expected to be offered a position on the board. What will remain is the Allergan brand.

"The Allergan brand remains," said Mr. Saunders. "We have to figure out the right context, in terms of the Actavis brand as well. The Allergan brand will exist."

Supplements Are Found Wanting in Formulas, Claims

Researchers analyzing popular eye vitamins to determine whether their formulations and claims are consistent with scientific findings determined that some of the top-selling products do not contain identical ingredient dosages to eye vitamin formulas proven effective in clinical trials. In addition, the study found that claims made on the products' promotional materials lack scientific evidence. The results of their study were published online in *Ophthalmology*, the journal of the American Academy of Ophthalmology.

Recommended treatment for age-related macular degeneration at certain stages of the disease includes nutritional supplements. The landmark Age-Related Eye Disease Study found in 2001 that a specific formula of nutritional supplements containing high doses of antioxidants and zinc could slow the worsening of AMD in those who have intermediate AMD and those with advanced AMD in only one eye. A follow-up study that concluded in 2011, AREDS2, determined that the formula was still effective if one ingredient, beta-carotene (a form of vitamin A), was replaced with related nutrients, lutein and zeaxanthin. Beta-carotene was substituted in AREDS2 due to its link to increased risk of lung cancer in smokers. The two studies prompted a surge in sales of eye supplements, which are marketed as containing the AREDS or AREDS2 formulas.

To test whether the products are consistent with the studies' findings, researchers compared the ingredients in top-selling brands to the exact formulas proven effective by AREDS and AREDS2. The researchers, based at Yale-New Haven Hospital-Waterbury Hospital, Penn State College of Medicine, Providence VA Medical Center and Warren Alpert Medical School of Brown University, identified the five top-selling brands based on market research collected from June 2011 to June 2012, and analyzed the brands' 11 products.

They found that, while all of the products studied contained the ingredients from the AREDS or AREDS2 formulas:

- Only four of the products had equivalent doses of AREDS or AREDS2 ingredients;
- Another four of the products contained lower doses of all the AREDS or AREDS2 ingredients;
- Four of the products also included additional vitamins, minerals and herbal extracts that are not part of the AREDS or AREDS2 formulas.

In addition, while all 11 of the products' promotional materials contained claims that the supplements "support," "protect," "help"

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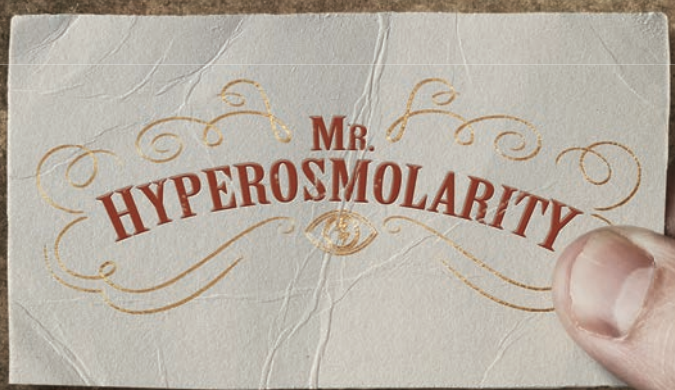

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or "promote" vision and eye health, none had statements specifying that nutritional supplements have only been proven effective in people with specific stages of AMD. There were also no statements clarifying that currently there is not sufficient evidence to support the routine use of nutritional supplements for primary prevention of eye diseases such as AMD and cataracts.

"With so many vitamins out there claiming to support eye health, it's very easy for patients to be misled into buying supplements that may not bring about the desired results," said first author Jennifer J. Yong, MD. "Our findings underscore the importance of ophthalmologists educating patients that they should only take the proven combination of nutrients and doses for AMD according to guidelines established by AREDS and AREDS2. It's also crucial that physicians remind patients that, at this time, vitamins have yet to be proven clinically effective in preventing the onset of eye diseases such as cataracts and AMD."

A results table of the analyzed products can be found at http://www.aao.org/newsroom/release/upload/Table-1-OcularNutritionalSupplements-InPress.pdf.

The AAO recommends ophthalmologists consider antioxidant vitamin and mineral supplementation, per the AREDS and AREDS2 trials, for patients with intermediate or advanced AMD. It also maintains that, based on the six-year timeframe of the AREDS trial, there is no evidence to support the use of these supplements for patients who have less than intermediate AMD. Ophthalmologists can read the Academy's AMD Preferred Practice Pattern guidelines at http://bit.ly/aaoamdppp. The public can learn more information about AMD and AREDS supplements at http://bit.ly/eyesmartamd. REVIEW

Ocular Nutritional Supplements: Are Their Ingredients and Manufacturers' Claims Evidence-Based?

BRAND (COMPANY)	PRODUCT	COMPARED TO AREDS INGREDIENTS*	COMPARED TO AREDS/AREDS2 DOSES**
PreserVision (Bausch + Lomb)	PreserVision Eye Vitamin AREDS Formula Tablets	Same	Same
	PreserVision Eye Vitamin AREDS Formula Soft Gels	Same	Same
	PreserVision Eye Vitamin Lutein Formula Soft Gels	- Beta-carotene + Lutein	Same
	PreserVision AREDS2 Formula	- Beta-carotene + Lutein + Zeaxanthin	Same
Ocuvite (Bausch + Lomb)	Ocuvite Eye Vitamin Adult 50+ Formula	- Beta-carotene + Lutein + Zeaxanthin + Omega-3 fatty acids	30% of Vitamin C 7.5% of Vitamin E 50% of Lutein 50% of Zeaxanthin 11% of Zinc 50% of Copper
	Ocuvite Lutein & Zeaxanthin Eye Vitamin and Mineral Supplements	- Beta-carotene + Lutein + Zeaxanthin	12% of Vitamin C 7.5% of Vitamin E 50% of Lutein/Zeaxanthin 19% of Zinc 100% of Copper
	Ocuvite Lutein Eye Vitamin and Mineral Supplement	+ Lutein + Selenium	40% of Vitamin C 15% of Vitamin E 4% of Beta-carotene 20% of Lutein 50% of Zinc 100% of Copper
ICaps (Alcon Laboratories)	ICAPS Eye Vitamin Lutein & Omega-3 Formula	+ Vitamin A as retinol (- beta-carotene) + Vitamin B1, B2, B3, B6, B9, B12 + Calcium + Selenium + Manganese + Lutein + Zeaxanthin + Omega-3 fatty acids	9% of Vitamin C 3% of Vitamin E 100% of Lutein 100% of Zeaxanthin 9% of Zinc 45% of Copper
	ICAPS Eye Vitamin Lutein & Zeaxanthin Formula	+ Riboflavin + Manganese + Selenium + Calcium	80% of Vitamin C 38% of Vitamin E 26% of Betacarotene 33% of Lutein/Zeaxanthin 75% of Zinc 200% of Copper
ICaps AREDS (Alcon Laboratories)	ICAPS Eye Vitamin AREDS Formula	Same	Same
EyeScience Macular Health Formula (EyeScience)	EyeScience Macular Health Formula	+ Vitamin D + Selenium + Vitamin B6, B9 + Lutein + Zeaxanthin + Bilberry extract + Alpha lipoic acid + Grapeseed extract + L-Glutathione + MacuGlo proprietary blend	100% of Vitamin C 100% of Vitamin E 100% of Lutein 100% of Zeaxanthin 50% of Zinc 100% of Copper

Per Packaged Facts, Rockville, MD, USA

*AREDS, Age-Related Eye Disease Study (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta-carotene, 80 mg of zinc, 2 mg of copper)

**AREDS2 (500 mg of vitamin C, 400 IU of vitamin E, 10 mg of lutein, 2 mg zeaxanthin, 80 mg of zinc, 2 mg of copper)

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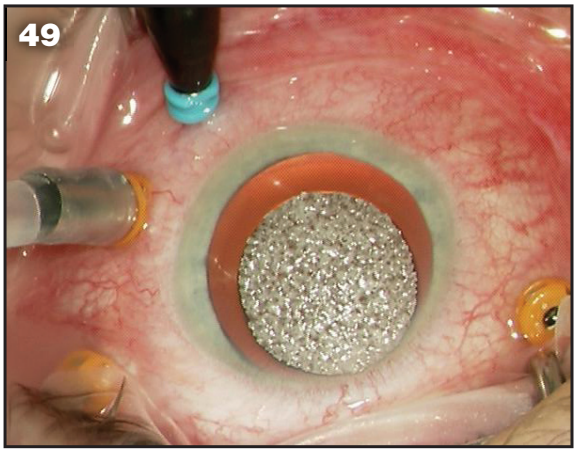

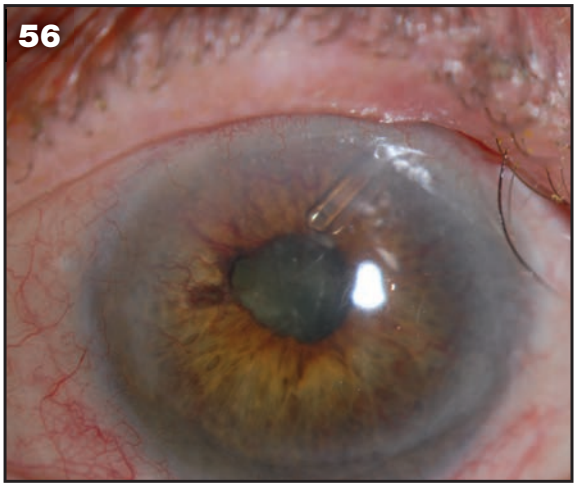

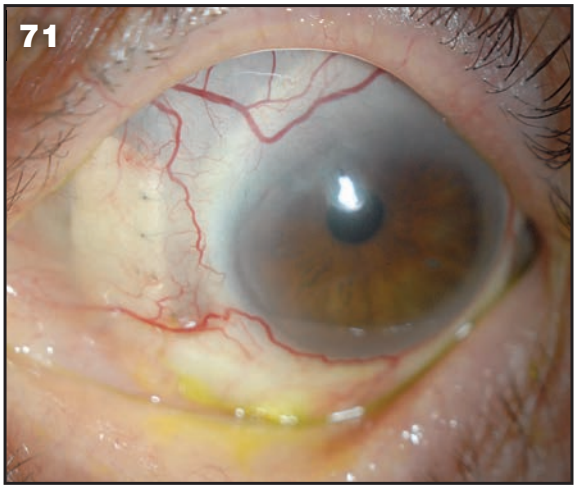

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This product should not be used in patients with a history of hypersensitivity to Bacitracin.

www.perrigobacitracin.com

Please see adjacent page for full prescribing information.

References: 1. Kempe CH. The use of antibacterial agents: summary of round table discussion. *Pediatrics*. 1955;15(2):221-230. **2.** Kowalski RP. Is antibiotic resistance a problem in the treatment of ophthalmic infections? *Expert Rev Ophthalmol*. 2013;8(2):119-126. **3.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123(3):341-346. **4.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol*. 2007;144(2):313-315. **5.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **6.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **7.** Data on file. Perrigo Company.

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To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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An Unblinking Look at the Past, An Insightful Look at the Blink

The Roman god Janus is often depicted as having two faces, to look forward and back, and is credited by some as the inspiration for our month of January. January is most often associated with looking ahead, but this month, we're true to Janus and his dual focus.

On the theory that the best way to prepare the future is to take the best of the past and learn from it, this month we offer a new department, Masters of Surgery (p. 44). The series will feature some of the leading surgeons and educators in ophthalmology, who will share their insights and the best ideas that they like to pass on to the residents and fellows fortunate enough to study with them. Thanks to Dr. Gary Abrams for kicking off the series this month; look for installments every other month as the year moves on. And a special thanks to Emmett Cunningham for bringing us the concept.

And in celebration of his 250th Therapeutic Topics column, by far our longest running contribution, Mark Abelson harkens back to the earliest days of translational research, even before the concept of bridging basic science and clinical application was fully defined. Dr. Abelson and his team have been instrumental in creating pathways from "bench to bedside." His column this month offers an intriguing real-world example of how translational scientists take a seemingly simple physiological action like the blink, and in their fashion, reverse engineer it back to the lab in pursuit of better, more effective treatment options.

We look forward to many, many more lessons from all of our masters.

REVIEW of Ophthalmology

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Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2014.

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Glaucoma: In Search Of the Perfect Stent

New *ab interno* devices in the pipeline offer novel advantages while addressing some of the limitations of earlier approaches.

Christopher Kent, Senior Editor

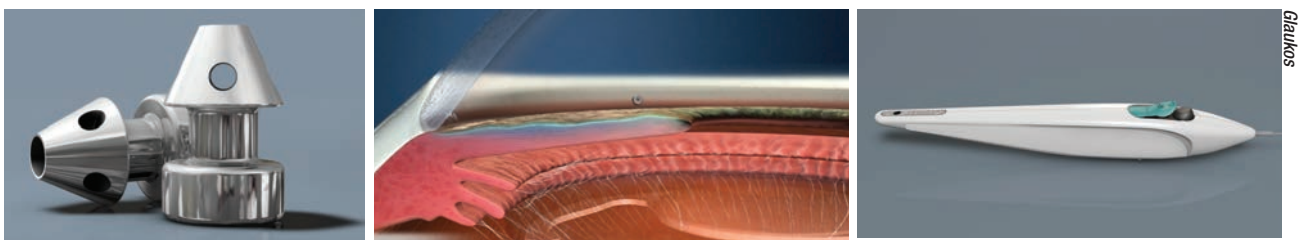
One area in ophthalmology that's currently seeing a lot of innovation is implantable devices designed to reduce intraocular pressure in glaucoma patients, with an emphasis on minimally invasive, *ab interno* procedures that can be combined with cataract surgery. Here, three surgeons who have experience using four different stents currently in the pipeline share their experience.

The iStent Inject

Most ophthalmic surgeons are familiar with the Glaukos iStent. One of two new iterations of this device, the iStent Inject, is now in clinical trials outside the United States. (The other, the iStent Supra, targets uveoscleral outflow and is also under investigation.) L. Jay Katz, MD, director of the Glaucoma Service at Wills Eye Hospital in Philadelphia, has experience using the iStent Inject.

Dr. Katz points out several differences between the currently available iStent and the iStent Inject. "Instead of being an L-shape, the second-generation device is shaped a little bit like a mushroom," he says. "Placement technique is also different. Instead of a venipuncture-like technique, the iStent Inject uses a straight-on approach, a little bit like a nail gun. You go directly onto the meshwork with the forceps delivery and push the little mushroom stent directly through the meshwork and into Schlemm's canal. Technically it's easier because you're going directly into where you think Schlemm's canal is, head-on, instead of trying to cannulate it.

"Another difference is that this device can be loaded with multiple stents," he continues. "Currently, two stents are preloaded into one delivery device. So you push one stent in, then move over and push the second stent in without exiting the eye. The nice thing about multiple stent placement is that we now have a multitude of studies showing that multiple stents do produce a lower IOP than a single stent does. That makes sense, since the outflow apparatus of the eye is circular and you have collector channels all along the perimeter draining from Schlemm's canal. The more access to the collector channels you have with multiple stents, the more pressure-lowering you'd expect, and the studies thus far indicate that this is the case."



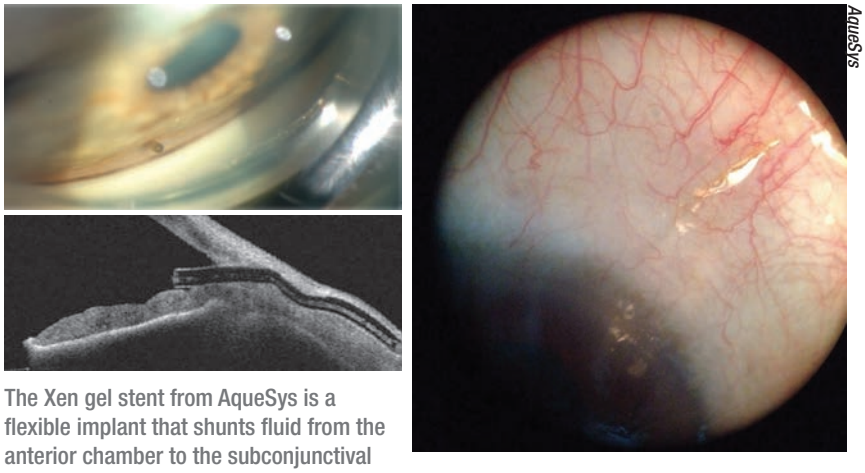
The iStent Inject from Glaukos—one of two new variations on the current iStent—is pushed directly through the trabecular meshwork into Schlemm's canal. The delivery device (above, right) can hold multiple stents, allowing multiple implants without exiting the eye.

This article has no commercial sponsorship.

Dr. Katz explains that although the device is experimental in the United States, he has implanted the iStent Inject as part of a multi-surgeon trial in Armenia. "As part of the protocol we were implanting both iStent versions in different patients, so it was easy to compare them," he says. "There's no question that, in my hands at least, the iStent Inject is a lot easier to use."

A recent randomized study sponsored by Glaukos compared treating open-angle glaucoma with a fixed combination of latanoprost/timolol vs. implantation of two iStent Inject devices in 192 subjects.[1] Both groups displayed a high safety profile, and both produced significant reductions (≥20 mmHg) in IOP. However, there was a 17.5-percent, statistically significant between-group difference in favor of the iStent Inject at the ≥50 percent level of IOP reduction. The authors concluded that using the iStent Inject was at least as effective as using two medications.

"Any time you have a new surgery, there's always a learning curve," adds Dr. Katz. "However, if you've already used the first version of the iStent you'll be ahead of the curve. A lot of the surgical novelty when using an iStent has to do with positioning the patient, holding a gonio lens, using different hand positions and inserting the device. All of these are essentially the same with the second-generation stent. The only thing that's a little different is that you have to learn how to push it into place just the right amount, and that requires some learning. But it's certainly a faster learning curve than with the first device."



The Xen gel stent from AqueSys is a flexible implant that shunts fluid from the anterior chamber to the subconjunctival space, creating a bleb, much like a trabeculectomy. The Xen stent, however, is implanted *ab interno* from across the eye through a clear cornea incision, in about 15 to 20 minutes.

The Xen Gel Stent

"The Xen gel stent [from AqueSys] is a soft, permanent, non-migrating, subconjunctival implant that shunts fluid from the anterior chamber to the subconjunctival space," explains Joseph F. Panarelli, MD, assistant professor of ophthalmology at Bascom Palmer Eye Institute, Miami. "It's a compressible and tissue-conforming hydrophilic implant made of porcine gelatin that's crosslinked with gluteraldehyde, a material that's been used for other medical purposes. The cylindrical, 6-mm long implant comes with three different-size lumens: 45 µm; 63 µm; and 140 µm.

"Most MIGS devices are designed to enhance normal aqueous outflow through the trabecular meshwork and Schlemm's canal," he notes. "This stent is different in that it bypasses the natural drainage pathway and can produce the lower intraocular pressures that we typically only get with trabeculectomy or tube shunt procedures. However, there are numerous potential advantages of the Xen gel stent over a trabeculectomy or tube shunt. It requires only 15 to 20 minutes to implant, gives you immediate intraocular pressure reduction and needs relatively little postoperative management. The small luminal diameter of this shunt seems to provide enough resistance to aqueous flow that postoperative hypotony is minimized, and this procedure may be combined with a subconjunctival injection of mitomycin-C to enhance long-term intraocular pressure control. Of course, like any new procedure, there is a learning curve that must be overcome at the outset."

Dr. Panarelli says that despite some similarity to trabeculectomy, the Xen gel stent can qualify as a MIGS procedure. "I believe it meets the five criteria specified by Ike Ahmed," he says. "It's inserted through a clear corneal microincision; it's minimally traumatic to the targeted tissue; it allows for rapid recovery with minimal impact on the patient's quality of life; and it has a good safety profile. The fifth criteria, efficacy, will be determined by the ongoing trials of the device, but having implanted it myself, I've seen that we can get reasonable intraocular pressure reduction with it. This device has the potential to help bridge the gap between medical treatment and filtering/tube shunt surgery."

Inserting the Xen Gel Stent

Dr. Panarelli says that to perform the basic procedure he begins sitting temporally. "I make a 2-mm temporal clear cornea incision about 180 degrees from where I want the device to be seated in the superonasal quadrant," he explains. "Then I take the inserter, which is similar to an IOL inserter, and enter the anterior chamber. The 27-ga. needle inserter tip should pierce the anterior portion of the trabecular meshwork; it is then advanced forward until it exits the sclera. The ideal 'landing spot' is

3 mm posterior to the limbus. While the implant is being delivered into the subconjunctival space, the needle slowly retracts. Gentle forward pressure is applied to keep the device from springing back into the anterior chamber. Once the stent is in place, a bleb will begin to form immediately.

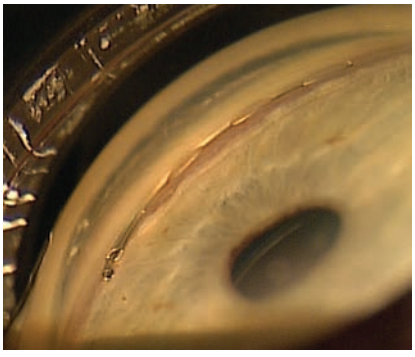
"Good preoperative gonioscopy is essential to successful implantation," he notes. "You need to make sure you have at least a grade-three open angle where you want to implant the device; you don't want a narrow angle or focal peripheral anterior synechiae. I always perform the procedure under a retrobulbar block because the patients may feel some pain when you insert and advance the device through the sclera."

Dr. Panarelli says the learning curve is similar to the other MIGS procedures, but may be a little easier. "Many of those procedures have to be done under direct gonioscopy; this one doesn't," he notes. "I do perform indirect gonioscopy to confirm where the needle is seated in the angle before advancing the device, but it's not a required part of the procedure. With experience, this procedure can be performed quickly and safely, but I suspect it will more often be performed by glaucoma surgeons rather than cataract surgeons as it may be better-suited to treating patients with moderate-to-advanced glaucoma."

The Hydrus Microstent

"The Hydrus Microstent from Ivantis is a novel, 8-mm long Schlemm's canal scaffold made out of nitinol, a biocompatible alloy," explains Hady Saheb, MD, MPH, assistant professor of ophthalmology and director of resident research at McGill University in Montreal. "It has two principal mechanisms: providing a bypass of the trabecular meshwork and scaffolding Schlemm's canal for three clock hours where it can access multiple collector channels. To implant the Hydrus, you approach the trabecular meshwork and Schlemm's canal under a gonio lens; with the inserter you puncture the trabecular meshwork and slide the device into the canal. Thus, part of the device is in the anterior chamber, while the majority of the device is in Schlemm's canal. This maintains a bypass of the trabecular meshwork similar to the iStent."

The Hydrus Microstent in inserted into Schlemm's canal, where it acts as both a scaffold for about three clock hours of the canal and a partial bypass of the trabecular meshwork.



Dr. Saheb says there are no published studies on the clinical efficacy of the Hydrus device yet. "However, there have been some basic science studies [sponsored by Ivantis]," he says. "The cadaver Schlemm's canal integrity study, which was a scanning electron microscopy study of Schlemm's canal in post-mortem eyes after insertion of the Hydrus device, showed integrity of the collector channels in the area of the Hydrus insertion.[2] Another study showed increased outflow in post-mortem human eyes after insertion of the Hydrus device at multiple IOP levels.[3] There was also a biocompatibility study which looked at inflammation and encapsulation after insertion of the Hydrus device in both nonhuman primates and rabbits; months after insertion the devices had caused minimal inflammation or encapsulation.[4] These three published studies suggest a good safety profile for this device, and promising effect."

Dr. Saheb adds that a number of clinical studies are currently under way, although none have been published in the peer-reviewed literature. "However, data reported at the meetings from randomized clinical trials and case series indicates that all the studies have so far found a significant reduction in IOP and medications after combined cataract surgery and Hydrus device implantation," he says. "They have also reported a safety profile similar to that of cataract surgery alone. Hopefully, the first randomized, controlled trial results will be published in the next year or two."

Dr. Saheb says he has implanted a number of the Hydrus stents himself. "My experience has been very positive," he says. "As with most *ab interno* surgeries, there is a learning curve to inserting the device properly, but that can be quite quick for those who have prior gonioscopic surgical skills."

The CyPass Micro-Stent

Dr. Saheb has also had limited experience with the CyPass Micro-Stent (Transcend Medical). "This is another *ab interno* glaucoma device," he says. "It's inserted through the angle into the supraciliary space, designed to take advantage of the negative pressure gradient between the suprachoroidal space and the anterior chamber. It's made from a polyimide material; it's 6.35 mm long, with an external diameter of 510 µm."

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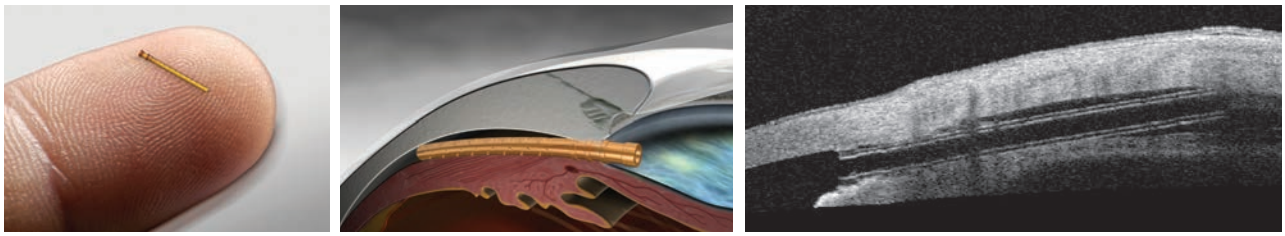

The CyPass Micro-Stent is placed between the scleral spur and the ciliary body, taking advantage of the negative pressure gradient between the suprachoroidal space and the anterior chamber. Surgeons report that the insertion is a straightforward process.

Dr. Saheb says the insertion is relatively simple compared to other *ab interno* devices. "You aim to place the device between the scleral spur and the ciliary body," he says. "It then slides along this potential space between the scleral spur, which becomes the internal scleral wall posteriorly, and the ciliary body, which becomes the choroid posteriorly. The potential space between the choroid and the sclera follows along that plane, and the junction of the scleral spur and the ciliary body is readily visible in the gonioscopic view. I found the surgery to be very straightforward.

"In terms of data, a recently published clinical study looked at 142 patients with open-angle glaucoma and cataract who underwent device implantation," he adds.[5] "They separated the cohorts into patients with a high baseline IOP and those with a low baseline IOP. They found that in the group with high baseline IOP there was a significant lowering of the IOP and number of medications. In the group with low baseline IOP, there was stabilization of IOP and a lowering of the number of meds. The safety profile was comparable to the safety of cataract surgery alone." REVIEW

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8:00am - 5:00pm
Reception to follow

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The Art of Implanting Multifocal Lenses

Christopher Kent, Senior Editor

Preoperative measurement accuracy and surgical precision are crucial to good outcomes.

Although not every cataract surgeon is eager to offer patients the option of multifocal intraocular lenses, a great many surgeons do. And as technology improves, and the familiar drawbacks to these lenses gradually become less of an issue, it's inevitable that more surgeons will come on board—at least until some other truly ideal way to correct presbyopia appears. Here, four experienced doctors offer their insights into the factors that produce a good outcome, with an emphasis on surgical issues.

Certainly one of the keys to success is careful measurement and planning—and a thorough knowledge of your own statistical track record with implanting these lenses. That knowledge can act as a guide to choosing how to proceed under any given set of circumstances. "If you can't deliver a perfectly emmetropic eye at the end of surgery, you have no business implanting a multifocal optic IOL," notes Robert M. Kershner, MD, MS, FACS, professor and chairman of the department of Ophthalmic Medical Technology at Palm Beach State College, and president and CEO of Eye Laser Consulting in Palm Beach Gardens, Fla. "These lenses are not very forgiving; there are a number of surgical steps the surgeon has to pay attention to before selecting these advanced optic designs.

"First and foremost, you have to do everything in your power to maximize the optical result," he says. "The step where you're most likely to err is in your preop planning. Preoperative biometry and lens selection require the surgeon to know his or her own stats and data points in order to achieve a high level of accuracy. In reality, the outcome of multifocal surgery is determined before the surgery rather than during the surgery. If you can execute what you've planned to do and obtain the predicted result, you'll have a happy patient."

Preexisting Conditions

Richard Mackool, MD, PC, director of the Mackool Eye Institute and Laser Center and senior attending surgeon at the New York Eye and Ear Infirmary, says the most common avoidable error that surgeons make is failing to detect a pre-existing condition such as corneal epithelial or endothelial dystrophy. "A careful slit-lamp exam is required to detect them," he notes. "It's not that this is a frequent mistake, but of those that are made, this seems to be number one.

"Epiretinal membranes are also very easy to overlook," he continues.

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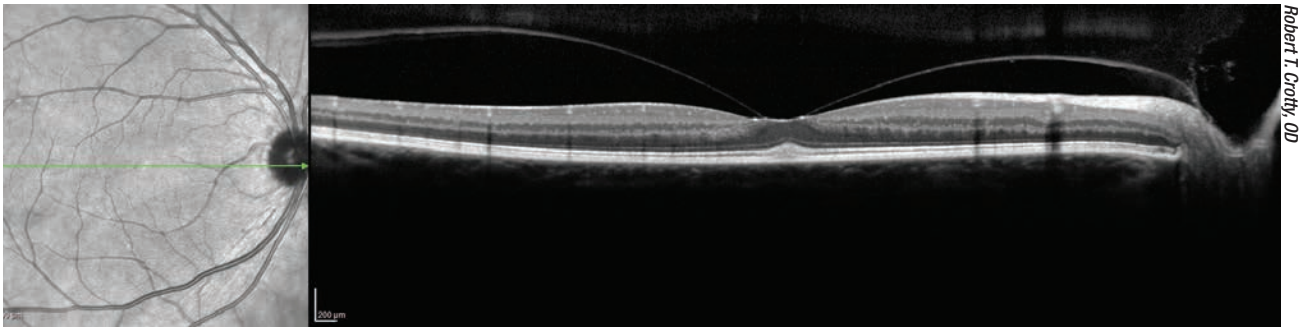


Robert T. Crotty, OD

Posterior vitreous separation with vitreal macular traction, on Heidelberg Spectralis OCT. This condition could undermine the outcome when implanting a multifocal IOL, and can be missed during a normal examination. This was caught because of further preop testing.

"Some surgeons routinely do macular OCTs in all patients before they implant a multifocal lens to avoid missing this. I don't fault them for doing that, but I don't think it's necessary in every patient. The vast majority of patients will have a normal retinal examination and the cataract will be consistent with the measured acuity. In that situation, I don't believe a macular OCT is necessary.

"On the other hand, if you have reason to suspect that there might be an epiretinal membrane, such as a questionable retinal exam or a disparity between the measured acuity and the density of the cataract, then by all means proceed and do a macular OCT preop," he says. "This is important, because if you put in a multifocal lens and later discover that there was a preexisting epiretinal membrane, and the patient is not happy with his postop acuity, the waters are muddied. You won't know whether the problem is being caused by the multifocal IOL, the epiretinal membrane or both."

R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, La., and clinical professor of ophthalmology at Louisiana State University and Tulane Schools of Medicine in New Orleans, agrees that preexisting conditions must be addressed, including dry eye. (Dr. Wallace has worked with multifocal IOLs since the first commercially available model—originally manufactured by the 3M Company—appeared.) "We have to treat the dry eye preoperatively and explain to these patients that they may need more intensive meds postop for quite a few months, because preservatives in the drops exacerbate preexisting dry eye," he says. "That can really affect multifocal vision."

Dr. Mackool notes that any symptoms like distorted or wavy vision are a clear tipoff that something is wrong. "You probably won't put a multifocal IOL in that patient, no matter what," he says. "In essence, anything that would lower the patient's expected postoperative acuity and contrast sensitivity is a potential contraindication. Not necessarily an absolute contraindication, but potentially so."

He adds that new multifocal lenses in the pipeline may alleviate these concerns. "The ReSTOR 2.5, which will probably be available in the United States in the next three to six months, provides distance acuity that is essentially the same as an aspheric monofocal lens," he says. "Studies of the lens's modulation transfer function show it to be virtually indistinguishable from an aspheric monofocal in this regard. So patients who would suffer from the loss of some contrast sensitivity associated with multifocal lenses would very likely do fine with this new lens."

Working with Astigmatism

"Correcting astigmatism is obviously critical to getting a great outcome with these patients," notes Dr. Wallace. "I've developed limbal relaxing incision instruments for Bausch + Lomb and Duckworth and Kent, and we spend a fair amount of time teaching surgeons to correct astigmatism using LRIs. Of course, the advent of femtosecond lasers has triggered a resurgence in interest in astigmatic keratotomy.

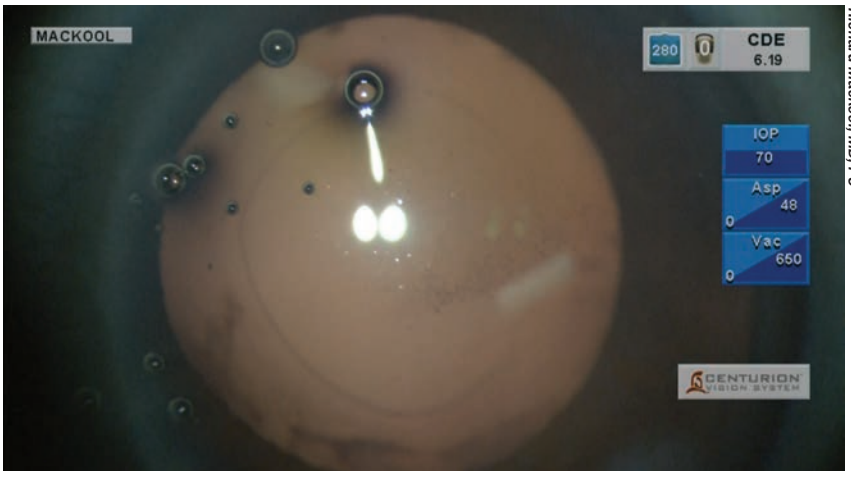
"In our experience, 2 D or less is a good limit for the amount of regular astigmatism correctable using LRIs," he continues. "If the patient is starting off with more than 2 D of astigmatism we can still implant a multifocal, but the expectation level of the patient has to be lowered. Yes, you can always touch up some of these patients with LASIK if the outcome isn't ideal, but that's expensive. It's better to let a patient with more than 2 D of astigmatism know that he or she is just not as good a candidate."

Dr. Wallace notes that special attention may be required if the Ks and corneal topography don't match up very well. "In those circumstances we will sometimes defer the LRIs until we see what the postop refraction in the first eye looks like," he explains. "That will tell us what to do for both eyes. If we determine that the eye still needs some astigmatic correction, we'll plan on doing LRIs in both eyes during the second eye's surgery. We prep both eyes preoperatively; once we're finished with the cataract surgery and I've done the LRIs on the second eye,

I reach over and put a lid speculum in the first eye, move the microscope over and take care of that eye as well. We've been doing this for years, and it's worked out quite well."

Irregular astigmatism is generally considered a contraindication for implanting a multifocal lens. "If the patient has irregular astigmatism before surgery, I think you're ill-advised to implant a multifocal optic," says Dr. Kershner. "You're not going to be able to control the refractive outcome. So if you cannot create a spherical cornea, you should set your postoperative goals to achieve functionality with another lens choice. Of course, if the patient ends up with irregular astigmatism that was not there before surgery, you must set out to correct the error. Find out where you went wrong and undo the damage. In most cases the error was present before the surgery, and was either missed in the preoperative workup, or made worse with an unrealistic surgical plan."

Both Robert T. Crotty, OD, clinical director of Wallace Eye Surgery, and his wife have had multifocal implants in their own eyes. Dr. Crotty notes that at Wallace Eye Surgery both preoperative corneal topography and WaveScan aberrometry are done on all multifocal candidates. "We're looking for increases in corneal aberration such as coma or astigmatism," he explains. "Some studies have reported that corneal coma values greater than 0.32 µm may result in increased dysphotopsia with the use of diffractive multifocal IOLs. In general, irregular astigmatism often makes the quality of postoperative vision unpredictable. We don't consider a patient who is demonstrating significant amounts of irregular astigmatism to be a candidate for a multifocal IOL."



Richard Mackool, MD, PC

An eye with corneal guttata. The corneal opacities reduce contrast sensitivity as well as BCVA when more advanced. Multifocal IOLs are generally not advisable for these patients.

Previous Refractive Surgery

An increasing number of patients who are interested in multifocal implants have had prior LASIK, PRK or RK. This presents a number of challenges. "Caution should be taken with patients who have had previous refractive surgery and are considering multifocal IOLs," says Dr. Crotty. "We've had a few cases of patients with previous radial keratotomy where we have implanted an accommodative intraocular lens with good success. We do believe that patients who have undergone refractive surgery, such as LASIK, PRK or RK, show many aberrations. However patients who were treated for 1.5 D or less of hyperopic LASIK, or 3 D or less of myopic LASIK may be considered candidates. In our experience, however, good quality in vision is harder to achieve due to their decreased contrast sensitivity."

"Previous corneal refractive surgery of any kind may have left the patient with—for lack of a better description—a multifocal cornea," notes Dr. Mackool. "If the patient had myopic LASIK, he will likely have some spherical aberration. If his pupil is small enough that the light rays coming in are essentially parallel, then that spherical aberration won't come into play; but if he doesn't have a small pupil, the spherical aberration is more likely to bother him. Similarly, irregular astigmatism is a relative contraindication because the more irregular the astigmatism, the greater the image degradation and the greater the need for a small pupil to be able to function well. (Of course, the amount of benefit you derive from having a smaller pupil is affected by the type of multifocal IOL you're implanting, because different multifocal IOLs function differently.) The message here is that not everyone who has had LASIK will have trouble with a multifocal implant, but the situation is less predictable.

"That means it's important to have a discussion with the patient so he understands what he's signing up for," Dr. Mackool continues. "If that individual is absolutely committed to the idea of trying a multifocal lens, he should understand there's a significant possibility that he'll need to use a miotic agent postoperatively to achieve satisfactory acuity, especially in the evening. His crystalline lens may have been compensating for whatever spherical aberration the LASIK left in the cornea, and the IOL may not do that. The IOL will also be smaller than the crystalline lens, which could make a difference.

"Most surgeons will be on the lookout for things like corneal epithelial dystrophy, irregular corneal surfaces

and macular degeneration," he adds. "All of those things can compromise the outcome of implanting a multifocal in a patient who is hoping and expecting to be spectacle-free. But subtle things like spherical aberration after myopic LASIK are also very important issues that need to be discussed with the patient."

Dr. Wallace notes another issue with post-LASIK candidates. "Because these individuals have already had refractive surgery, they tend to have higher expectations," he says. "They expect everything to be perfect. We have to let them know that of all the people we see, they may be the least predictable in terms of outcome. Because they've had a change in corneal shape, we have to use fudge factors in the IOL power calculation formulas in order to give them decent results. So we talk to these patients about possibly having to add a piggyback lens later if we don't get the result we want. It's important to lower their expectation level."

Is Femtosecond the Answer?

"Femtosecond laser cataract surgery is exciting technology, and I think it will continue to get better as time goes by," says Dr. Kershner. "It has its detractors, but then people badmouthed phaco when it first came out, too. Unfortunately, though, many surgeons look to the femtosecond laser as a way to compensate for their lack of reproducibility and precision when creating corneal incisions and capsulorhexes. I don't believe the femtosecond laser is going to be the solution to those concerns."

Dr. Kershner offers several reasons femtosecond laser technology may not be a major advantage when it comes to fine-tuning cataract surgery for better multifocal outcomes:

• ***Computer accuracy is no guarantee of a good outcome.*** "One of the problems with this technology is that it will do whatever you tell it to and accomplish that with great precision, but it's only as good as your ability to know what you want it to do," he says. "Yes, the femtosecond laser can make an incision with incredible accuracy, just as an excimer laser can remove tissue to the level of 0.25 of a micron. All it's going to do, though, is make you repeat your mistakes more precisely.

"I've seen published pictures of femtosecond laser astigmatic keratotomy and clear corneal incisions that were clean and beautiful—but not in the right places," he notes. "They were perfect arcs, and centered at the corneal limbus, but not centered exactly over the pupil. They looked good, but would they have produced a perfect refractive outcome? Not a chance. The whole point of incision placement is to maximize the refractive enhancement and minimize the refractive error.

"When it comes to the capsulotomy, something I know a lot about, there is yet to be a published study that demonstrates that—assuming the lens is centered—the perfectly round, centered capsulorhexis made with a femtosecond laser results in better visual outcomes than an irregular, continuous tear capsulorhexis," he adds. "Indeed, there are studies that show that the incidence of inadvertent capsular tears is greater with the sawtooth edge of a femtosecond capsulotomy than with a continuous smooth-tear capsulorhexis."

• ***A manual capsulorhexis provides information about the capsule that a laser capsulotomy does not.*** "Back in 1994 I developed the first capsulorhexis cystotome forceps," says Dr. Kershner. "That simplified the capsular tear by letting the surgeon open the capsule and create the tear with a single instrument through a 1-mm incision. The added benefit of never letting go of the anterior capsular flap was to give the surgeon the op-

portunity to assess the capsule. We used to call it 'reading the capsule.'

"The anterior lens capsule is a true basement membrane, with an anterior layer of simple cuboidal epithelial cells beneath it," he explains. "Being composed of Type IV collagen and glycosaminoglycans, it is normally quite elastic. At only 14 µm in thickness (ranging from about 8 to 28 µm) it is thickest anteriorly and thinnest posteriorly where there are no cells. Because there are no cells on the posterior lens capsule, it is at least half as thick as the anterior lens capsule. When you're manually tearing the anterior capsule you can feel the nature of it. Is it elastic or brittle? Does it tear rapidly or slowly? This gives you insight into the nature of the posterior capsule. Thus, if you get an inadvertent posterior capsule rupture at the beginning of a case, you will have seen it coming because you had the ability to read the capsule. With femto technology, the surgeon is separated from his surgical field."

Richard Mackool, MD, PC

Anterior capsule with clear areas (lens epithelium removed) adjacent to darker areas where lens epithelium is still present. Removal of subcapsular lens epithelium greatly delays postoperative adhesion of the capsule to the IOL. This facilitates later IOL exchange, should this become necessary due to unusual problems such as persistent glare or haloes.

Even a perfectly round capsulorhexis is only as good as what you do before and after it and how you implant the lens. "Both zonular integrity and capsular strength are critical to centration of the IOL," Dr. Kershner says. "If you have any suggestion that the zonules have been compromised or that the capsule is gossamer thin, irregular or oval-shaped, it is not going to suspend the lens in the center and you should not be implanting a multifocal lens. A spherical lens may be a better choice, as it will allow you to proceed without complications. A multifocal lens will not.

"I would argue that a continuous-tear capsulorhexis with a smooth edge over 360 degrees has better structural integrity than a femto capsulorhexis made with today's technology," he adds. "If I want to ensure a perfectly smooth-edged capsulorhexis, I can deliver a better one with a manual cystotome forceps capsulotomy than with a laser. The laser opening will look prettier, be absolutely accurate in placement and be the exact size you want, but will it be superior to the one we create manually? The answer is no."

Preoperative Pearls

These strategies will help ensure a good outcome when implanting a multifocal IOL:

• ***If you're just starting to offer multifocal lenses, prepare before jumping in.*** Dr. Mackool offers some advice to surgeons who may be considering offering multifocal implants to their patients. "First, choose your initial patients wisely," he says. "Choose those who are highly motivated, have small pupils and no other potentially complicating factors such as more than 1 D of astigmatism. Second, have your plans in order for what you'll do when a patient is not happy. What procedure will you use if you don't get rid of his astigmatism and/or other refractive error? PRK? LASIK? Limbal relaxing incisions? You don't want to be saying, 'Oh, I'm not sure what to do; let me find a doctor who can take care of this for you.' Yes, if the problem is vitreoretinal, you'll likely want to send the patient to a vitreoretinal specialist, but most problems will be refractive issues. The more prepared you are to deal with those, the better. Third, have a clear presentation regarding the multifocal lens options, and rehearse it before you actually present it to any patients. I suspect that many surgeons offering these lenses for the first time haven't thought this through. Fourth, have a handout available for the patient to read before she sees you. My patients read four pages of information about multifocal IOLs—or toric lenses, if they have astigmatism—before they

see me for the exam."

• ***Check pupil size and function before the patient is dilated.*** "Pupil size is definitely an issue because each multifocal is slightly different," notes Dr. Kershner. "The entrance pupil will dictate which part of the refractive surface is being utilized under any given lighting condition. If you don't check the function of the pupillary sphincter under different lighting conditions—scotopic, mesopic and photopic—you are going to get burned. That's why the surgeon should never see these patients post-dilation, the way most ophthalmologists do. You really need to see how the physiology of their eyes works firsthand before anyone has pharmacologically altered them. This is critical with these patients."

• ***Don't wait to manage pupil size issues postoperatively.*** "Some doctors manage pupil size issues reactively rather than proactively," says Dr. Kershner. "If the pupil needs to be smaller to improve vision after the implantation, they say 'I'll just put you on pilocarpine.' That's not an answer. I think it's much better to determine what the patient's pupil size and function is before the surgery rather than trying to fix the problem after the fact with drugs or a laser."

• ***Get the most accurate biometry possible.*** "Whether you use laser interferometry or ultrasonic biometry, you need to know the precise dimensions that light travels through to the fovea, down to a hundredth of a millimeter," says Dr. Kershner. "That means accurately measuring the anterior chamber depth, distance from the central lens to the fovea and axial length of the eye. Unfortunately, many surgeons rely upon averages when making their IOL calculations; they figure it's close enough. The reality is, some patients have a very shallow anterior segment and very deep posterior segment. Others are the reverse. Where we expect to place the IOL within the capsular bag does not always correlate with the actual nodal point of the eye. Admittedly, current formulas don't allow us to maximize the value of this information, but it's valuable information, nonetheless."

Dr. Kershner notes that the lens manufacturers are beginning to respond to the need for more precision. "This is reflected in many lens manufacturers now offering these lenses in quarter-diopter steps," he points out. "I've argued for years that every lens should be labeled with its exact power, instead of rounding the power to the nearest half-diopter and putting that on the box. If every IOL manufacturer were to label the actual power of each lens in the box, then we could select the individual lens that's as close as possible to what we need, which would further improve our outcomes."

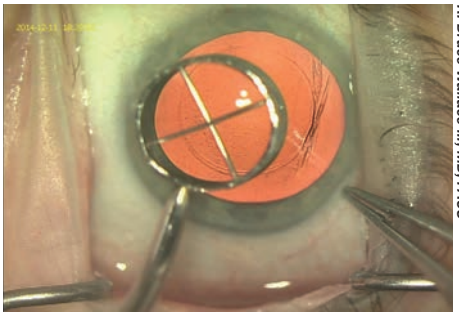
• ***Consider doing OCT on all of these patients.*** "You definitely want to check for any retinal pathology," says Dr. Crotty. "Sometimes if you're dealing with a fairly dense cataract it's not that easy to see. You might miss a subtle epiretinal membrane, early stages of macular hole development or macular degeneration. In many cases if we're suspicious we will send out for a retinal consult. If you proceed on the assumption that everything is fine and implant a multifocal, and then the patient actually has retinal pathology, there's no way you're going to be able to convince the patient that it was there before surgery."

• ***Pay close attention to the details.*** Dr. Crotty notes that it's crucial to have a preop protocol for these patients and pay attention to the details. "You don't want to look back and think, 'I shouldn't have put this lens in,'" he says. "Simple things like the condition of the ocular surface will impact the outcome. If you cannot get that ocular surface pristine, then that patient is not a candidate for a multifocal lens. When I see unhappy patients who came to us from another prac-

tice, it's generally because somebody didn't pay close enough attention to the details."

• ***If the cornea could be a potential problem, don't do a quick fix and proceed to implant a multifocal.*** "I recently read about a surgeon who addressed the problem of a less-than-ideal corneal surface by applying an amniotic membrane for a few days to heal the cornea, and then proceeded to implant a premium lens," says Dr. Kershner. "I think this is shortsighted. We all would agree that the treatment of corneal surface dry-eye disease, meibomitis, blepharitis and the like, is critical before attempting any intraocular surgery. Unless the surgeon is confident that an irregular corneal refractive surface is completely and permanently corrected, any advanced optic IOL is contraindicated. The adverse conditions that created that problem in the first place didn't permanently go away just because you put a membrane graft on for three days or the patient used topical antibiotics for a month. Whatever underlying disease processes are present need to be fully addressed, or you can be assured that they will come back to haunt you."

• ***Plan your primary incision carefully.*** Dr. Kershner says incision construction is a potential source of trouble. "It's very important that the surgeon pay particular attention to incision construction and placement and its planned effect in altering corneal topography," he notes. "I've been performing astigmatic keratotomy for decades. Based upon a very large body of accumulated data, the refractive results of our astigmatic keratotomy and surgical incision placement are quite predictable. The fact is, any time you incise the cornea you are changing the corneal topography—period. If the surgeon fails to take into account the position, size, length and geometry of the surgical incision for cataract removal, irrespective of what tools will be used to create the incision, the refractive outcome will not achieve target goals. There are surgeons who say, 'I'm not too worried about that because I can always do a touchup with LASIK.' The problem with this reasoning is that the patient may never give you the opportunity to go back and make up for any refractive shortcomings. The surgeon must be absolutely confident that what he thinks he is going to get is exactly what the patient ends up with."



R. Bruce Wallace III, MD, FACS

A corneal marker can act as a guide, constraining the diameter of the capsulorhexis. This ensures that the capsule will overlap the edge of the IOL optic, stabilizing the implant.

Intraoperative Pearls

• ***Video every surgery.*** "A key part of my effort to fine-tune my surgical outcomes is to monitor what we are doing while we are doing it," says Dr. Kershner. "From a practical standpoint, you haven't had someone in the operating room critiquing your technique since you were a resident. But that doesn't mean you can't honestly critique yourself. The only way to do that is to sit back and review every surgery that you have done at the end of the day by watching the digital recording. Then, when you are absolutely confident of reproducibility and an unexpected outcome occurs, you can go back and review the recording of the surgery to see if anything was done that could have caused the aberrant outcome, and whether you could have done anything to avoid it. If we find the smoking gun, we need to change what we are doing so that it never happens again."

• ***Don't overstretch the pupil.*** "Multifocal lens patients usually benefit from having a small pupil," notes Dr. Mackool. "You don't want to wind up with a big pupil, so stretching small pupils with retractors or rings is not a good idea. A lot of those pupils won't return to their normal, desirable small size. It's better to use iris retractors and only enlarge the pupil to the minimum size necessary for the procedure. For me, that's about 4.5 mm. Of course, it depends on the technique you're using. But if you're doing phaco chop and dividing the nucleus into small segments, you don't really need a large pupil to get through the case."

• ***Consider using a corneal marker to help create the capsulorhexis.*** "We use a 6-mm optical zone corneal marker to mark the corneal surface—with the center of the optical zone as the central visual axis—to guide us in the intended placement and size of the capsulorhexis," says Dr. Wallace. *(See picture, above.)* "We described this technique in a 2003 article.[1] When making the manual capsulorhexis we stay just inside that visual guide, almost always producing a 5- to 5.5-mm capsulotomy. This method isn't as precise as a femtosecond laser, but it works pretty well, and we haven't found the precision of the capsulorhexis to be a major issue in our outcomes. However, we feel that using a guide is important in terms of refractive outcomes because you want the capsule to overlap the optic so it doesn't move around inside the eye and cause changes in the refraction postop. Using the guide ensures that that happens."

Dr. Wallace notes that even though this concern is less consequential when implanting a monofocal lens, he still uses the marker on every cataract patient. "Using the same technique on a regular basis allows for a greater amount of consistency," he points out.

"You get used to using the tool and become more confident that you can do what you need to do when it matters the most—when you're working with a multifocal patient."

• ***Make sure any future lens exchange will be as easy as possible.*** "You should anticipate that you might have to exchange the multifocal lens," says Dr. Mackool. "That means that you want to do whatever you can to facilitate that removal. There are basically two things that will facilitate an IOL exchange: First, aim to have the edges of the capsulorhexis overlap the optic by 0.5 mm or more in all meridians. If the capsulorhexis is larger than the optic, the anterior and posterior capsule will fuse together, often very tightly; separating them can be difficult and can result in opening the posterior capsule.

"Second, it's very desirable to remove epithelial cells from the undersurface of the anterior capsule," he adds. "You don't have to do it for 360 degrees; 180 degrees is plenty. Doing that greatly delays adherence of the anterior capsule to the surface of the IOL optic. This makes it much easier to perform the viscodissection maneuver that's needed to free the IOL from the capsule so the implant can be removed without damaging the capsule, and a new implant can be placed in the capsular sac." *(See picture, p. 28.)*

• ***Center the lens.*** Dr. Kershner points out that the intracapsular positioning of a multifocal lens is far more critical than it ever was with monofocal lenses. "With spherical lenses, if you were slightly off-center, if the capsular opening into the bag wasn't completely round or there was zonular dehiscence, the lens optic would still be forgiving," he points out. "With multifocal and toric optics, that's not the case. These lenses demand perfect centration and planar positioning to function optimally. If you can't deliver that, you shouldn't be implanting them."

Dr. Wallace says he likes the middle of the optic to be about half a millimeter nasal. "The sweet spot is not in the middle of the pupil," he notes. "Fortunately, these lenses tend to stick pretty well; they don't move that much."

• ***Be aware that you might have to deal with "retinal astigmatism."*** "A patient may have a posterior staphyloma, which can create retinal astigmatism, a term I coined back in 1973," says Dr. Mackool. "I became aware of this issue back in the days of intracapsular cataract surgery. We'd remove the cataract and then measure the patient for spectacles postoperatively. I found that a lot of patients with long, myopic eyes would have a disparity between their corneal astigmatism and their refractive astigmatism, in both amount and axis. In fact, there were patients with no corneal astigmatism who had significant refractive astigmatism. It turned out that they had a posterior staphyloma and a tilted retina, and they needed an astigmatic correction to see better. That's the condition I call retinal astigmatism.

"Unfortunately, there is no way to measure this when the crystalline lens is still in place," he continues. "So the only way to determine the presence or absence of that condition—which of course you need to correct if your aim is the best possible uncorrected acuity—is to measure the vision after the cataract is removed by using the ORA device or doing an aphakic refraction outside the operating room, which would mean leaving the patient aphakic for a while. We do that commonly on patients who have had corneal refractive procedures or have keratoconus, to determine their required IOL power and amount of astigmatism. If we find significant astigmatism, we can manage it using limbal relaxing incisions or a toric IOL. It can also be addressed with a corneal refractive procedure at a later date."

(continued on page 38)

IOL Alternatives To Multifocality

Walter Bethke, Managing Editor

Avoiding glare and halo while expanding focal depth is the primary goal of these implants.

For many cataract patients, multifocal intraocular lenses have worked well and have afforded them a broader range of vision postoperatively. For others, though, the possibility of glare, halo and other qualitative vision problems has led them to shy away from multifocal lenses and stick with monofocal options. There are some lenses, however, that aim to bridge the gap between multifocals and monofocals and allow more vision at different distances while minimizing visual side effects. Here's a look at the mechanism of action and current results of these devices.

Lenses in Use

There are a few IOLs in use in the United States and/or abroad that may give increased depth of field without qualitative issues.

• ***AMO Tecnis Symfony.*** In June 2014, AMO received the CE Mark to market the Tecnis Symfony Extended Range of Vision IOL in Europe. The Symfony takes a different approach to maximizing a patient's range of vision by addressing the optical property known as chromatic aberration.

Because it tackles this chromatic aberration, the Symfony is an example of an emerging class of IOL known as the extended-depth-of-focus lens.

Abbott Medical Optics

The AMO Symfony lens expands depth of field while also addressing chromatic aberration that can decrease acuity.

Though the nomenclature has yet to solidify, surgeons say the current hallmark of the EDOF lens is that it gives cataract patients a somewhat expanded depth of field without the drawbacks associated with a multifocal visual system.

Jack T. Holladay, MD, MSEE, FACS, a clinical professor of ophthalmology at Houston's Baylor College of

Medicine, says the EDOF lens may fill a niche for certain surgeons and patients. "About 8 percent of the lenses used today are multifocals," he says. "The reason for this relatively low usage is a result of the typical surgeon not wanting the possibility of a lens exchange if the patient has intolerable halos or glare. This isn't the end of the world, but it is another surgery, there are costs involved, the patient often goes to another doctor for this, et cetera. So, for this surgeon, it's easier to put in a non-multifocal lens where the risk is that if the patient doesn't have adequate near vision you can give him a pair of reading glasses. The EDOF lens will perform better at near distances than the monofocal, but not as well at near as the multifocal. But, halos and glare will be comparable to the monofocal."

To understand how the Symfony can give more depth of field, it helps to understand the natural steps of accommodation, surgeons say, because the lens actually builds on them to get its effect. "When we look up close, we experience the depth-of-field effect," explains Dr. Holladay. "Our pupils constrict. That constriction ends up giving us the equivalent of about 0.75 to 1 D more near vision than we'd have when looking into the distance because of the pinhole effect."

Building on this natural accommodative effect, the Symfony uses diffractive optics to both improve the quality of vision from the lens and expand the range of distances the lens at which the lens can adequately focus. "The first thing to understand is that the term diffractive optics doesn't necessarily imply multifocality," says Daniel Chang, MD, an ophthalmologist from Bakersfield, Calif., who is an investigator for the U.S. trial of the Symfony. "This is not a multifocal lens, but it does use diffractive optics to do two things: First, it corrects chromatic aberration. Second, it uses these optics to extend the range of quality vision." As Drs. Holladay and Chang explain it, with optics you can't gain an expanded range of vision without losing something in terms of the sharpness of vision; this is just the nature of the beast. However, by correcting chromatic aberration, even without using diffractive optics to expand the visual range, the lens would have extremely sharp distance vision on the order of 20/12 or even 20/10. The process is not yet done, however, in the Symfony. The diffractive optics are then used to expand the range of vision. Expanding the depth of focus degrades the tack-sharp "starting point" (something must be lost, as Dr. Chang pointed out), but since the lens started with such sharp vision, it only degrades to about the level of 20/20. "So the amount you degrade takes you back to the level of a good monofocal IOL," Dr. Chang says.

The idea behind chromatic aberration correction is simply to get the colors of the spectrum focused at the same point. "The different colors of the spectrum focus differently," Dr. Chang explains. "Different materials have different dispersive properties with light; some focus colors closely together and some spread them out. The idea is that if you focus all of the colors together, you can have a higher quality of vision. The Symfony takes the AMO acrylic that focuses colors well—meaning it has a low dispersion—and improves upon it."

Dr. Chang says he can't discuss any of the current FDA results, but based on information from New Zealand and Europe, the Symfony gives 20/20 or better vision at distance over a range of about 1.5 D, and 20/40 or better over a range of 2.5 D. "Ninety-six percent of patients had 20/25 or better vision at intermediate," he says. "At near, 92 percent have 20/40 or better vision. In terms of quality of vision, it's comparable to a monofocal from a night vision and a contrast sensitivity perspective." The U.S. FDA trial of the Symfony lens is ongoing.

• ***Bausch + Lomb Crystalens AO and Trulign Toric.*** One of the originals from the first wave of presbyopic lenses, the Crystalens doesn't need much introduction. Though surgeons and patients achieve varying degrees of near vision from the proposed forward movement of the lens due to its flexible, hinged haptics, Crystalens doesn't pose the risk of visual problems such as halo or contrast sensitivity loss that can crop up with a multifocal lens. The Crystalens AO has prolate, aspheric optics that are free of spherical aberration. There's also a toric version of the lens, the Trulign.

In a recent study of 78 patients randomized to receive the Crystalens AO, the Alcon ReSTOR +3 D or the Tecnis Multifocal, the Crystalens patients had significantly fewer halos than the Tecnis, and less optical scatter than either the ReSTOR or the Tecnis MF.[1] Though binocular uncorrected distance acuity wasn't significantly different among the lenses, the AO had better monocular and binocular uncorrected and distance-corrected intermediate acuity than the ReSTOR or the Tecnis MF. However, the ReSTOR and the Tecnis MF had better uncorrected and distance-corrected near acuity than the Crystalens.[1]

Bloomington, Minn., surgeon Y. Ralph Chu has been implanting the Crystalens, in addition to other premium IOLs, for more than 10 years, and says his approach to the lens has evolved over time. "While I believe multifocal IOLs can be effective, it's hard to predict who's going to be very unhappy with the loss of quality of vision that they have," Dr. Chu says. "For that reason, I feel like offering a lens that has a lower risk of these issues, yet still gives some extended range of focus, is something patients understand and appreciate.

"Our discussion with candidates for presbyopic IOLs has changed," Dr. Chu continues. "We used to give those

talks [from the podium] about patient selection, but we've evolved into educating all patients about their options. There is no perfect lens platform out there right now, so patients have to understand the limitations of the technology and see how it would fit into their lifestyle. Having that education is more important than saying, 'You drive a truck so you shouldn't get this type of lens.' "

As to what a patient's postop near vision will be, Dr. Chu says his view of this has evolved, also. "I see it as an individualized process vs. a specific endpoint," he says, "because we know there are people who see 20/20 and J1 with a multifocal who are unhappy and we've had patients with great intermediate and distance vision, but who still wear readers, who are very happy. I really emphasize it's a binocular system, and our goal is to use both eyes together. We try to understand at what distance the patient needs to see and achieve that goal for him. We will actually say that there's a possibility of wearing glasses at some distance for some activities, and this goes for any lens platform.

"I don't target getting everyone to 20/20 and J1 because it may not be what some want," he continues. "Some want to see the computer and at distance and are fine with wearing a light reader, while some might like the computer and near vision distances and are fine wearing glasses for distance." Dr. Chu says he'll often employ monovision with the Crystalens to boost the near vision. "We'll work in a little mini-monovision, setting the non-dominant eye for a little more near," he says. "That's a great technique to help maximize the range that patients get with the Crystalens. We customize it to the patient; there's no one set way we treat every Crystalens patient."

The Crystalens platform also gives surgeons an option for treating a patient's astigmatism in the form of the Trulign IOL. In the FDA study of the Trulign, it achieved an average reduction in cylinder of 86 percent, with 78 percent of the patients ending up within 0.5 D of the intended refraction. In terms of postop rotation, there was an average rotation of less than 2 degrees between four and six months postop. Ninety-seven percent of eyes rotated 5 degrees or less.[2] "The Crystalens design, with its haptics and rectangular shape, fits a toric platform well," opines Dr. Chu. "It's been incredibly stable rotationally."

• ***Monofocal IOLs with some depth of focus.*** Over the years, surgeons have noted that some monofocal IOL patients will achieve more depth of focus than one would think possible with a touch of monovision. "A study from 30 years ago[3] using monofocal lenses showed that if you shoot for about -0.25 to -0.75 D, many patients could read without correction postoperatively with monofocal IOLs," says Dr. Holladay.

One monofocal lens that's gotten some buzz for its near effect is the Lenstec Softec HD, a flexible acrylic IOL with an aspheric optical design on both the front and back surfaces. At the 2011 meeting of the American Society of Cataract and Refractive Surgery, Tampa, Fla., surgeon Jim Gills reported on a study from his practice in which 28 percent of Softec HD patients could read J3 [20/40] or better uncorrected monocularly.

Los Angeles surgeon Paul Dougherty says he's experienced similar results. "The lens is composed of the same material as the Tetraflex [accommodating IOL]," says Dr. Dougherty, who thinks this may contribute somewhat to the lens's apparent ability to give a better range of vision in some patients. "Though these patients don't get full accommodation, I don't need to do as much monovision on them as I would with a pure conventional monofocal lens to get them out of reading glasses. If we set them for distance, they'll get distance and maybe some intermediate vision, but they'll still need reading glasses."


Lenstec

The Softec HD lens is available in 0.25-D steps to enhance accuracy.

Lenses in the Pipeline

In addition to the handful of non-multifocal lenses that can expand patients' range of vision, there are also other innovative designs in the works.

• ***Calhoun Vision Light-adjustable Lens.*** The LAL's design is unique in that its power is adjustable by the surgeon, with input from the patient, after the lens is in place. The adjustment is made by irradiating the lens's special silicone material with ultraviolet light, which changes the lens's shape and therefore its power. The same light is then used to lock in the shape change when the refraction is optimal. The LAL is currently in a U.S. FDA trial.

An interesting application of the adjustability of the LAL is using it to induce special aspheric changes to the lens, broadening a patient's range of vision. Calhoun calls this process adjustable blended vision.

Tijuana surgeon Arturo Chayet, who consults for Calhoun Vision and has used ABV in patients, explains how the process works. "The idea is to bring the patient to emmetropia and then add asphericity to the optical component of the lens," he says. "The protocol typically calls for the dominant eye to be adjusted for low asphericity, and the non-dominant eye

For allergic conjunctivitis[1]

THE POWER TO CALM THE ITCH

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INDICATION 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.

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 the accompanying prescribing information for BEPREVE® on the following page.

Reference: 1. BEPREVE [package insert]. Tampa, FL: Bausch + Lomb, Inc; 2012.

BAUSCH + LOMB

For product-related questions and concerns, call **1-800-323-0000** or visit **www.bepreve.com**.

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BEPREVE®
(bepotastine besilate ophthalmic solution) 1.5%

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

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H1 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 Bausch & Lomb Incorporated. at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

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 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 BEPREVE.

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

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

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 during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. 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 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses 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 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled 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 1,000 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.

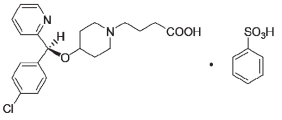
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection 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 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 times 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 below the quantifiable limit (2 ng/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 topical ocular use in humans).

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 3,300 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 a 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 size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE
Store at 15º – 25ºC (59º – 77ºF).

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.

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Tampa, FL 33637
Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

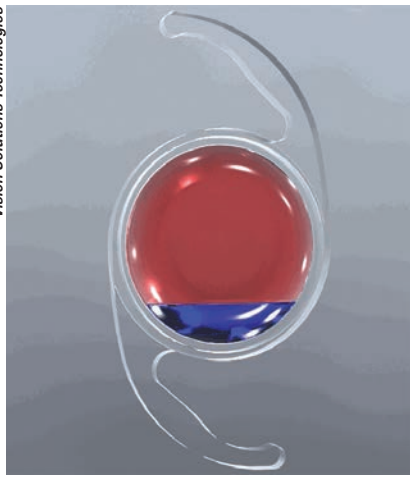
US/BEP/13/0028 4/13

for high asphericity, with the goal being all three ranges of vision. Typically the dominant eye will be set for distance and the non-dominant for near, and both together will give good intermediate vision. In the non-dominant eye, they give up a little distance vision for more near vision, so it's typically around 20/32 uncorrected in that eye for distance, but it will be able to read J2 or J3."

In a study of binocular vision results in 20 ABV patients at Dr. Chayet's practice, 75 percent could see 20/16 or better at distance after lock-in. Eighty-five percent now see 20/20 or better and 100 percent see 20/32 or better. In terms of binocular intermediate vision at 60 cm, 60 percent see J1+ versus zero patients preop, 75 percent see J1 versus 20 percent at this level preop and 100 percent see J2 or better compared to 45 percent preop. Ninety percent see J2 or better binocularly at near (40 cm) versus 15 percent preop. Fifty-five percent now see at least J1, compared to 5 percent who could see that well preop.

• ***PowerVision FluidVision lens***. The FluidVision lens is an acrylic IOL with anterior and posterior optics with a central cavity between them. The compressible haptics contain a silicone-oil-based fluid. Paul Roux, MD, of Pretoria, South Africa, is the lead investigator on the FluidVision's latest international study, and says the haptics work together with the eye's natural processes to aid accommodation. "The two large haptics are connected to the central fluid cavity," Dr. Roux explains. "When the eye's normal physiological accommodation occurs and the zonules release tension on the capsule, it compresses the two large haptics. This pushes the silicone fluid between the two optics and creates an accommodative effect."

In a pilot study of the lens, 20 patients underwent monocular implantation with it. At six months, uncorrected distance vision averaged slightly better than 20/20, intermediate averaged 20/25 and near averaged 20/33. "The average objective accommodation measured is just under 2 D," says Dr. Roux. "The subjective accommodation is actually more, around 2.5 D, because of pupil size reduction during accommodation. This effect appears to be lasting.



Vision Solutions Technologies

The Vision Solutions' Liquilens uses two immiscible liquids as part of its solution to presbyopia. When the patient looks down, the fluids' interplay introduces a new index of refraction that boosts near vision.

At this stage, the one thing about the lens that's slightly unpredictable is the initial refraction after you've put it in," Dr. Roux adds. "Initially, we'd have a patient who was -2 or +1 postop. It's taken some changes to get the initial refraction as close to plano as possible. Now the majority of patients are within 1 D of emmetropia."

Right now, the lens injector goes through a 4-mm incision. "It's a large lens because it's got to fill the bag," explains Dr. Roux. "That's the basis on which it works. However, there's a drive to make that smaller, to around 3.5 mm or even less."

• ***Akkolens Lumina.*** Similar to the way the FluidVision lens uses physiological processes in its operation, the Lumina is a dual-optic lens that relies on the action of the ciliary body for its effect.

Alicante, Spain, ophthalmologist and Lumina researcher Jorge Alio says one of the keys to the lens's mechanism is its placement in the sulcus, which allows it to move. "The sulcus is stable and isn't influenced by fibrosis," he says. "We have a paper that's been accepted for publication in the *Journal of Refractive Surgery* in which we implanted the lens in the sulcus of one group of non-human primates and in the capsular bag in another group. After six months, the lens in the capsular bag is totally blocked but the lenses in the sulcus are still working.

"Once in the sulcus, action of the ciliary body causes one of the optics to slide over the other optic, creating a continuous change in the total lens power," Dr. Alio continues. "Currently, the limits of accommodation in the pilot study have been between 1.5 and 6 D, and the effect has remained at one year. Obviously, a lot still has to be demonstrated to use the lens clinically on a standard basis. I think it will accommodate 2 to 3 D easily, probably more in some cases."

Dr. Alio says the study has included 75 cases, 55 with the Lumina and 20 monofocal lens controls. Though the exact results are currently confidential, he says the distance vision is similar to that of a monofocal IOL and that intermediate is very good, owing to the fact that 2 to 3 D of power is helpful with intermediate distances. "Near vision is good," he says. "Even though some patients find 1.75 D to be a little less than necessary to keep near vision sustained, we have many who can see at near without glasses. The safety results are confidential, but initial expectations are that it might cause some pigment dispersion or increase IOP by interacting with the ciliary body. Even though we haven't had a problem with IOP increase, it's being carefully investigated and is one of the issues that will be followed up in more detail. Since

(continued on page 38)

(continued from page 31)

Postop Pearls

• ***Expect to YAG earlier than with other patients.*** "Multifocal patients who end up needing YAG laser treatment tend to need it earlier than monofocal lens patients," says Dr. Wallace. "Of course, many of these patients are younger than your average patient, so their capsules will tend to opacify sooner. Also, they usually lose their near vision first. The capsule may not appear to be that bad, but they'll be complaining about having trouble reading up close."

• ***When analyzing your pooled, cumulative, postoperative outcomes data, don't ignore the surgical outcome outliers—learn from them.*** In all my years as a surgeon, I've yet to have a big postoperative surprise," says Dr. Kershner. "It's not because I am so wonderful a surgeon, it's simply that I carefully analyze the results of what I am doing. This is one of the key things I have consistently done in my practice to optimize my results. I don't ignore the outliers when they occur, and I don't blame the patient. I assume that we either missed something in our surgical plan or did something other than what we should have done. Today it's easy to track all of your pre- and postop results to see exactly what you're getting. Create the graphs, look at the scatterplots and the range of errors and see how closely your outcomes matched your expectations. The dots that don't fall on the line are the outcomes that are the most important to increasing refractive precision.

"Patients are wowed by our technology," he adds. "Today they expect their cataract to be removed by a laser. But I like to point out to my patients that a good surgical outcome depends as much on the surgeon as on cutting-edge technology. When something does not go according to plan, it's the surgeon's experience that saves the day, not the technology. A million-dollar laser is like a sophisticated fly-by-wire jumbo jetliner; it's the experience of the operator that makes the technology work. When a flock of seagulls shuts down both of your jet engines on takeoff, it's the experience of a senior pilot like 'Sully' Sullenberger that saves the passengers and airplane. And how do you get that experience? It's not how many surgeries you've done; it's how carefully you have monitored them. It makes all the difference. So don't ignore your outliers, focus on them and learn from them." REVIEW

1. Wallace RB III. Capsulotomy diameter mark. J Cataract Refract Surg 2003;29:1866-1868.

(continued from page 37)

the lens is in the sulcus, we expected a high incidence of PCO, but so far it's only been 6 percent."

• ***Vision Solutions Technologies' Liquilens.*** Also taking the liquid route to accommodation is a lens invented by Rockville, Md., optometrist Alan Glazier. However, instead of relying on the body's anatomical forces, the lens uses gravity.

"Liquilens is kind of like putting on a reader," Dr. Glazier explains. "It uses the fluidics of two immiscible optically clear biocompatible fluids and their interplay to introduce an additional index of refraction into the line of sight that provides additional power when the patient looks down at a 60 to 70 degree angle." When the patient looks forward the fluid is out of the way and the lens provides distance vision. "One thing that some lens designers miss is that the act of reading isn't only an act of having near vision but sustaining it over time," Dr. Glazier says. "You have to have accommodation to see a certain distance but you need a certain amount in reserve, as well. So, to shoot for 2.5 D of focus, you might get that and the patient would be able to glance and see something, but the act of reading requires him to sustain that. To do that, you need extra power." Dr. Glazier says the lens has been able to achieve 9 D of accommodation in lab bench testing.

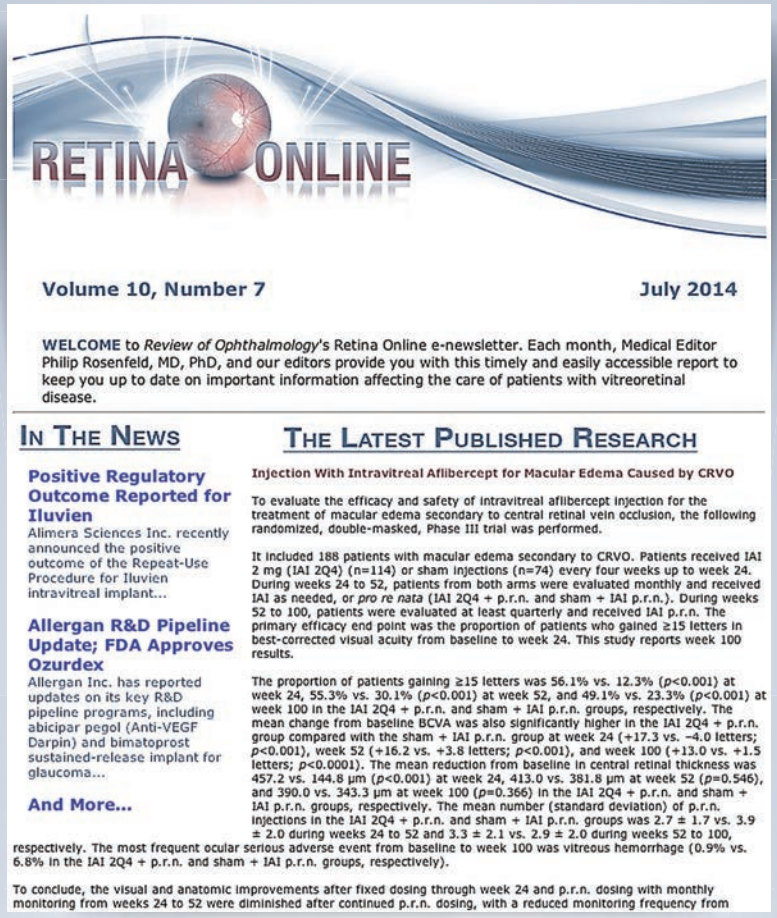
Intermediate vision won't be strong at the outset, though. "In the lens we're planning on entering the market with, it's like a bifocal so it won't have much intermediate vision," Dr. Glazier says. "But we have patents on designs that will provide intermediate in second- and third-generation products." Dr. Glazier is seeking CE certification for the lens in Europe.

In the future, Dr. Chang says some of the innovations occurring today will work their way into common ophthalmic parlance. "Chromatic aberration is an issue that most surgeons don't commonly think about, but correcting it can make a difference," he says. "It's kind of like 15 years ago when researchers began talking about spherical aberration and physicians were mystified. However, when we started correcting for it, it made a difference and people appreciated it. Chromatic aberration is basically the other half of that story." REVIEW

Drs. Holladay and Chang are consultants for AMO, Dr. Dougherty owns stock in Lenstec, Dr. Chayet consults for Calhoun Vision and Dr. Chu is a consultant to Bausch + Lomb. Dr. Alio and Dr. Roux are consultants to Akkolens and PowerVision, respectively. Dr. Glazier owns the rights to the Liquilens.

1. Pepose JS, Qazi MA, Chu R, Stahl J. A prospective randomized clinical evaluation of 3 presbyopia-correcting intraocular lenses after cataract extraction. Am J Ophthalmol 2014;158:3:436-46.
2. http://tinyurl.com/qfp7omf. The FDA Medical Devices Advisory Committee on the Trulign IOL. Accessed 11 Dec 2014.
3. Boerner CF, Thrasher BH. Results of monovision correction in bilateral pseudophakes. J Am Intraoc Implant Soc 1984;10:1:49-50.

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

Volume 10, Number 7 July 2014

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

Positive Regulatory Outcome Reported for Iluvien
Alimera Sciences Inc. recently announced the positive outcome of the Repeat-Use Procedure for Iluvien intravitreal implant...

Allergan R&D Pipeline Update; FDA Approves Ozurdex
Allergan Inc. has reported updates on its key R&D pipeline programs, including abicipar pegol (Anti-VEGF Darpin) and bimatoprost sustained-release implant for glaucoma...

And More...

THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

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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REVIEW® of Ophthalmology

Surgeons Seek Presbyopia Solution

Walter Bethke, Managing Editor

Surgeons say presbyopic lenses are fine, but say they're tiring of the trade-offs in vision.

Though 72 percent of the surgeons on our e-survey say they implant presbyopic intraocular lenses—and 64 percent say they're satisfied with their presbyopic lens outcomes—12 percent of the surgeons say they're unsatisfied with the lenses' performance, which is a slight increase over last year's survey. Ophthalmologists say the lenses usually give good outcomes, but can be very demanding in terms of preop calculations, and unforgiving if anything is slightly off, and they muse that maybe the ideal presbyopic lens solution is yet to arrive.

Surgeons' views on presbyopic lenses are just one facet of the lens topics tackled in this month's e-survey on IOLs. The e-mail survey was opened by 1,699 of the 11,708 subscribers to *Review*'s electronic mail service (14.5 percent open rate) and, of those, 99 surgeons (6 percent) shared their responses.

Presbyopic IOLs

Surgeons are very interested in offering patients a lens solution to their presbyopia, with 72 percent saying they offer presbyopic lenses in their practice.

On this year's survey, 23 percent of the surgeons say they're very satisfied with the presbyopic lens they use the most, and 41 percent say they're satisfied with it. On the other end, a quarter of surgeons say they're only somewhat satisfied with their presbyopic lens of choice, with another 12 percent identifying as unsatisfied with their lens—this is up from 5 percent who said they were unsatisfied with their presbyopic lenses in last year's survey. In terms of the lenses surgeons use most often, 41 percent say they use the Alcon

Surgeons Rank the Features of IOLs

Surgeons ranked IOL features from 6 (most valuable) to 1 (least valuable). Shown here is the average score for each IOL feature.

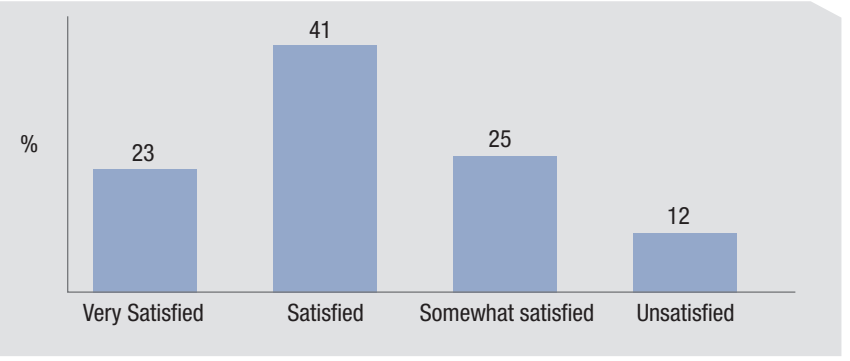
ReSTOR, 32 percent use the Tecnis Multifocal and 27 percent reach for the Crystalens first.

Though many surgeons use these lenses, they note that there's room for improvement in the designs. "Reading performance is good," says George Walters, MD, of Port Arthur, Texas, who uses the Tecnis Multifocal most often. "But a newer model with a lower add would be beneficial." A surgeon from Tennessee who implants all three brands of IOLs says they "work for the right patient, with appropriate expectations and realistic goals." A California surgeon who primarily implants the ReSTOR feels certain visual ranges could be improved with multifocals in general. "They work well, but suffer from poorer intermediate vision compared to distance and reading," he says. "There's glare at night, and they function poorly in dim light for reading. These aspects could be improved." Brad Ballard, MD, of Ft. Knox, Ky., says there can be problems, but you can head them off ahead of time. "Most people are happy," Dr. Ballard says. "But I prepare them by setting low expectations and I'm very selective about who can get one of these lenses."

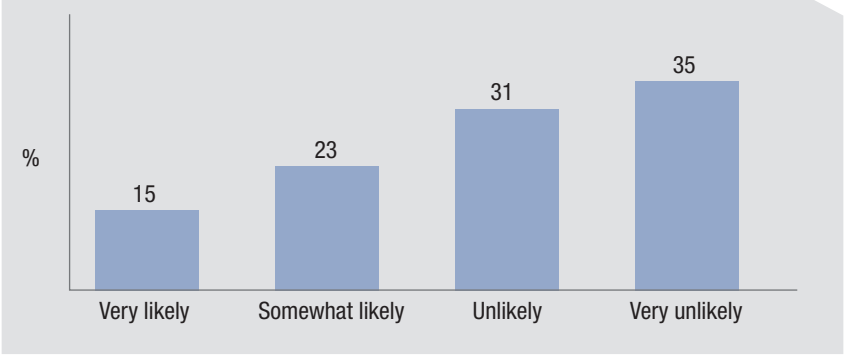
A vocal minority of doctors doesn't like the qualitative vision issues that patients may experience with multifocal lenses. "I'm very happy with it," says a surgeon from Pennsylvania. "I'd like to see a lens that has fewer halos at night." Another surgeon from Pennsylvania thinks some new designs are in order. "There's a diminished quality of vision and contrast sensitivity," he says. "They should make a lens with optics like those in multifocal contact lenses." An Iowa surgeon is on the fence about these lenses. "Some people just don't see well and require an IOL exchange, and then they are happy," he says. "I wish I could tell who this would be first. I'm almost thinking of stopping offering them. It just seems like it's such a downer for them and for us."

Looking ahead, 15 percent of surgeons who don't currently use presbyopic IOLs say they're very likely to use them within two years. Twenty-three percent are somewhat likely to do so. Thirty-one percent say they're unlikely to begin using them (compared to 26 percent last year) and 35 percent say they're very unlikely to start implanting them, which is a large increase from last year's 11 percent. "I'll use presbyopic IOLs if a truly accommodative lens becomes available," says Luther Fry, MD, of Garden City, Kan. "I won't use multifocals." One surgeon doesn't think the technology is there yet. "I am not satisfied with the results we can achieve with these lenses and I'm unsatisfied with the methods we have to correct things if and when a patient is not happy," he says. "A lens exchange after a YAG is a risky procedure." A surgeon from Arizona thinks they have potential, but isn't going to take the plunge yet. "When they work, they're great!" he says. "But the slightest lens power miscalculation leads to big problems."

Satisfaction with Presbyopic IOLs



Likelihood of Using Presbyopic IOL Within Two Years



Toric Lenses

Toric IOLs remain one of the most popular types of premium lens, with 75 percent of the respondents saying they implant them. Most of the surgeons are very pleased with the outcomes torics achieve. Sixty-one percent of the surgeons say toric outcomes are excellent, 31 percent rate them as fair and only 9 percent call them poor.

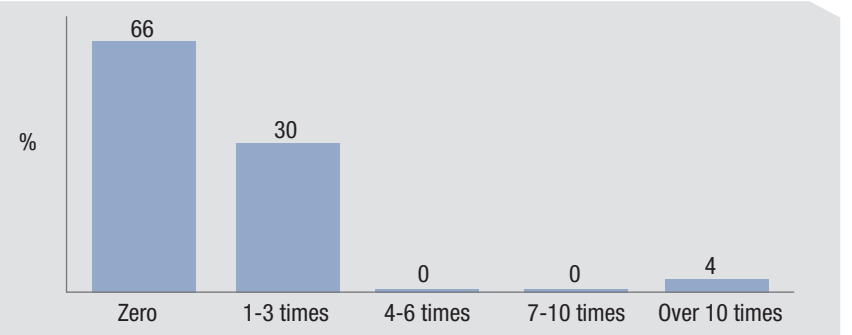
"In appropriate patients, the torics are excellent. If implanted properly, there is no downside to correcting

corneal astigmatism," says one surgeon who chose to remain anonymous. "In keratoconus patients who are stable over a few years with regular astigmatism, and don't plan on using postoperative RGP lenses, I will consider a toric as well." Robert Mobley, MD, of Clinton Township, Mich., also thinks they work well in the right patients, as well. "Toric lenses are highly recommended for greater than 1 D of against-the-rule astigmatism or greater than 1.25 D of with-the-rule astigmatism," he says.

A surgeon from Indiana says torics are good lenses, but surgeons should undertake implanting them with their eyes open to possible challenges. "Toric IOLs work," he says. "However, they present a challenging value proposition, because they require just as much, or more, surgeon acumen and diagnostic equipment savvy and more surgical work, as other IOLs do. Their cost is significant to patients because of that. Also, patients will still need glasses postop, so patient goals can't be completely met with them, especially for the price." A surgeon from Iowa agrees, saying, "You've got to get everything right—including posterior corneal astigmatism. This seems easy but is actually very demanding and requires regimentation and discipline." Dr. Fry likes them, but thinks expense is an issue. "I recommend them for everyone with over 1 D of cylinder," he says. "I provide free LRIs for 1 D or less. Unfortunately, [toric lenses] are too expensive and many patients can't, or won't, afford them. I wish they were around $200, so we could provide them to our patients affordably."

A couple of surgeons lament that, despite torics' popularity and overall good results, they're not always completely accurate. "I still usually get 0.5 to 0.75 D of cylinder in patients' refraction afterwards," says a surgeon from California, "despite seemingly accurate measurements and good axis placement."

Frequency of Suturing an IOL in a Year



Lens Design

In terms of the monofocal lens surgeons use for most of their cases, 51 percent use the Alcon IQ Aspheric, 26 percent prefer the AMO Tecnis and 6 percent use the Bausch + Lomb Akreos MICS lens. The Lenstec Softec HD and B+L enVista are next with 3 percent of the vote each, and with 2 percent of the vote each are the B+L SofPort AO, the Hoya iSymm/iSert, the Rayner C-flex and the B+L Akreos AO.

A surgeon from Los Angeles says he likes using the IQ Aspheric. "It's easy to implant, rotate and center," he says. A Tecnis user from New Jersey says, "It has been reliable and the patients are happy," while Texas' Dr. Walters, who prefers the B+L Akreos MICS lens, says, "It centers well and the patient can get pseudo-accommodation. It's very biocompatible with no discolorations or glistenings."

Managing Problems

To get a handle on how often things go awry with IOLs, surgeons were also asked about times when they had to suture-fixate a lens or explant one. Two-thirds of the respondents say they never have to suture a lens in any given year, 30 percent say they have to suture one to three lenses and 4 percent say they do it more than 10 times.

Surgeons give a variety of reasons for suturing the lenses. "I'll use iris suture fixation due to poor capsular support," avers Juan Nieto, MD, of Dubuque, Iowa. Steven Safran, MD, of Lawrenceville, N.J., says he often gets referrals for lens fixation. "I do it for patients referred in with a dislocated lens or an anterior chamber IOL that needs to be exchanged," he says. Some surgeons are even beginning to move away from sutures to a new method of fixation. "I'm tending toward a glue technique for PC-IOL fixation more often than sutures now," says a surgeon from Illinois.

Surgeons say lenses sometimes need to be explanted, as well. The most common reasons for explantation cited are:

- incorrect lens power;
- dislocation;
- poor vision/glare from a multifocal lens;
- IOL damage; and
- trauma.

Kentucky's Dr. Ballard recalls one instance when the implantation and explantation occurred the same day. "I implanted the wrong intraocular lens during surgery," he says. "Two minutes after the patient's transfer to the post-procedure care unit, I wheeled her back to the OR and explanted the lens and implanted the correct one." REVIEW



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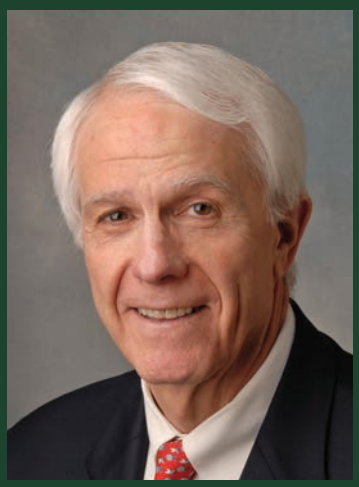
Teach Your Fellows **Well**

Voices—and even lyrics—**from the past** still ring true when it comes to preparing the next generation of eye surgeons.



By Gary Abrams, MD

In their classic 1970 song "Teach Your Children," Crosby, Stills, Nash & Young sang, "You, who are on the road, must have a code that you can live by." Good advice, whether on the road or doing vitreoretinal surgery! Hardly a day goes by in the operating room that I don't remember some rule or technique passed on to me by a former mentor. When applying cryotherapy to a retinal break, I always hear Tom Aaberg Sr. telling me, "Never cryo unsupported retina" (for fear of necrotic retinal breaks) and "Don't move the cryo probe until it defrosts" (because of the risk of fracturing a choroidal vessel). When putting in a scleral suture, I still hear Victor Curtin tell me to "pick with the tip of the needle" (to engage the sclera and set the depth) "and then glide" (through the sclera).

Surgery is a complex series of technical steps bound within an overall approach to surgery. Early in our careers, we learn those steps and approaches from mentors and hope to gather the tools to learn or create new techniques and approaches as we gain experience and advance in our careers. In this article on training vitreoretinal fellows, I took much from the mentors who trained me and much from observing the best fellows in the world over 35 years of teaching in Miami, Milwaukee and Detroit. From my mentors I learned to examine the eye (Ed Norton), develop a surgical plan (Robert Machemer) and carry out that plan (Tom Aaberg Sr. and Victor Curtin). From my fellows I have learned that there are many ways of accomplishing surgical goals and that the fellow's ability to think and adapt both before and during a case is usually more important than his or her technical dexterity. Herein are some of the rules I teach to my vitreoretinal fellows.

1. Be a good examiner and understand the pathology of the eye.

Edward W. D. Norton, the former chair and director of the Bascom Palmer Eye Institute in Miami, was the best examiner I have ever known. He used to play a game with fellows in which he always found something on the eye examination that the fellow missed. As a fellow, I took it as a challenge and spent extra time on each of his patients to try to identify every tuft, rosette or opacity, but while my skills definitely improved, I never bested him. From him, not only did I learn how to do a complete examination, I learned the importance of a complete examination.

One of the first things I teach a fellow is to understand the eye. I want the fellow to know the vitreoretinal relationship in any surgical case. In a rhegmatogenous retinal detachment, is the vitreous completely separat-

ed? Is the vitreous base posteriorly located? Is there a PVD at all? The answers to these questions will often determine the approach to repairing the retinal detachment. For example, if the retinal detachment is due to round holes in lattice degeneration in a younger patient without a PVD, a primary vitrectomy might not be the best approach for repairing the retinal detachment and a primary scleral buckle would be the preferred operation. In vitrectomy for diabetic traction retinal detachment, the character of the vitreoretinal adhesions (focal or broad) and the degree of vitreous separation anterior to and between the vitreoretinal adhesions will determine the difficulty of dissection. The examination of the eye in conjunction with the OCT will define the best areas for beginning peeling of epiretinal membranes. I prefer the fellow make a drawing of each case and bring pertinent studies, such as OCTs, to surgery.

Seeing the results of surgery and dealing with people after surgery is the best teacher!

2. Prepare for surgery.

Following clinic, Robert Machemer would sit with the fellows and discuss each case that was to have vitrectomy. He would discuss the pertinent pathoanatomy of the eyes and the approach to surgery. As I assumed my own surgical practice, I learned that I was best prepared for a case if I preoperatively went through an exercise of thinking through the case from beginning to end. I would close my eyes and visualize the pathoanatomy of the eye and how I would do each consecutive step of the operation. I would think in detail, such as how I expected the vitreous to separate, how I would dissect and remove membranes and how I would reattach the retina and how I would perform retinopexy. I would think of whether to do or revise a scleral buckle and whether to use perfluorocarbon liquids, gas or silicone oil. With this exercise, I soon found that I could anticipate potential problems in the case and best be prepared to deal with them. I still go through the exercise when I approach a particularly complex or difficult case. In addition to discussions with me prior to a case, I ask my fellows to go through the exercise of preoperatively visualizing the surgery on every case they do.

Besides the mental preparation for surgery, I want the fellow to prepare physically as well. The fellow should go through a checklist to make sure that everything needed for the case is available in the operating room. While a large medical center operating room may have multiples of every piece of equipment, that may not be the case everywhere. Therefore, it is the surgeon's responsibility to make sure all needed equipment is available. It is best to do this before the patient reaches the operating room because it is difficult to cancel a case once the patient is there. In addition, the fellow must learn to understand the equipment and be able to troubleshoot problems. The surgeon can't always depend on "others" to get balky equipment running or make sure all the tubes are correctly connected if the "others" aren't there.

3. Learn to operate.

It is difficult to learn vitreoretinal surgery by reading about it or watching it. The small nuances of vitreoretinal surgery are such that the fellow has to do surgery in order to learn surgery. The learning should be in a well-supervised environment. After watching one case with me, I give the fellow increasing surgical responsibilities on subsequent cases. Fellows vary in the time it takes to assume major technical and decision-making responsibilities, but the majority of motivated fellows learn to do most maneuvers in vitreoretinal surgery within six to eight months. Learning good decision-making generally takes more time than learning the technical aspects of retinal surgery. Decision-making only comes with reading, discussion of cases with mentors and thinking through each case prior to surgery. Post-surgery critique by mentors is critical to developing excellent technical and decision-making skills. Possibly most important, the fellow must see and follow all of his or her postoperative patients. Seeing the results of surgery and dealing with people after surgery is the best teacher of all!

In modern vitreoretinal surgery, there are many ways to reattach retinas, peel membranes or do many different maneuvers. At the American Academy of Ophthalmology Subspecialty Day in Retina, there are often debates on surgical topics with one speaker "pro" and the other speaker "con." Topics such as use of perfluorocarbon liquid to reattach the retina during vitrectomy vs. creation of a

drainage retinotomy, placement of a scleral buckle or not when doing primary vitrectomy for retinal detachment or whether a primary scleral buckle or a primary vitrectomy is best for a certain retinal detachment show that there is usually not a single general answer for most of these controversies. However, what is apparent is that the surgeon must be well-trained in all of these techniques so he or she can give the best treatment for the individual case based on best evidence.

4. Continue to learn.

Fellowship is only a beginning. I encourage fellows to continue to discuss cases with colleagues and mentors long after completion of fellowship. In addition, soon after completion of fellowship, I encourage fellows to observe outstanding surgeons operate. Unlike when first learning vitreoretinal surgery, a trained surgeon can learn a great deal by watching other surgeons operate. When new techniques are introduced, I encourage former fellows to go to seminars, observe videos and watch other surgeons in order to learn new techniques. Within one year of completing my fellowship, because of improvements in instrumentation, I was doing many things differently.

Vitreoretinal surgery is an always-evolving specialty and we must all continue to evolve as surgeons. Going back to Crosby, Stills, Nash & Young, " … and so become yourself because the past is just a goodbye." Ciao. REVIEW

Dr. Abrams is a professor at the Kresge Eye Institute, Department of Ophthalmology, at Wayne State University School of Medicine. Contact Dr. Abrams at: Kresge Eye Institute, Wayne State University, 4717 St. Antoine St., Detroit, Mich. 48201. Email: gabrams@med.wayne.edu.

REVIEW Calendar

FEBRUARY

5 - 8
HO CHI MINH CITY, VIETNAM
The Inaugural Asia-Australia Congress on Controversies in Ophthalmology will raise the most dynamic and controversial topics facing clinicians in the field, with the aim of reaching up-to-date and agreed-upon answers to ongoing debates in ophthalmology through evidence-based medicine and expert opinion. The Congress will emphasize issues related to the region in terms of retina, anterior segment, glaucoma, diagnostics, typical complications and distinctive responses to treatments. The official conference language is English. For more information, email cophyaa@comtecmed.com or visit comtecmed.com/cophy/AA/2015.

12 - 15
AVENTURA, FLA.
The American Society of Cataract and Refractive Surgery and American Society of Ophthalmic Administrator's Side X Side Conference, formerly known as Winter Update, will take place at Turnberry Isle Miami hotel and spa, in Aventura, Fla. This newly designed meeting has been specifically created for anterior segment eye surgeons and busy ophthalmic practice administrators who need in-depth, focused information on key topics that will allow them to integrate advanced techniques into their practices. Each year, Side X Side will focus on key innovations in the ophthalmic practice, providing in-depth "how to's" on all aspects, from discussions with patients, to preoperative screening and planning, to technique adjustments. Side X Side will incorporate the relaxed atmosphere and extensive interaction between faculty and attendees, both within sessions and at networking events, that the ASCRS/ASOA Winter Update made its own. CME and CE are available. For more information, call (703) 591-2220 or visit sidexside.ascrs.org.

MARCH

26 - 29
SORRENTO, ITALY
The 6th World Congress on Controversies in Ophthalmology will take place at the Hilton Sorrento Palace in Sorrento, Italy. This educational Congress will continue to focus on anterior segment, glaucoma and retina sections, and will also discuss controversies in other areas of ophthalmology, such as neuro-ophthalmology. The scientific program will include state-of-the-art lectures and controversial debates; outstanding world leaders as faculty will present both pro and con positions while further challenging and exploring what the optimal treatments for patients are, with emphasis on the appropriate use of new and emerging drugs. This format includes a substantial allocation of time for interactive debates and questions from the audience to each panel of experts. The official language of the Congress is English. For more information, email cophy@comtecmed.com or visit comtecmed.com/cophy/2015.

APRIL

15 - 17
SAN DIEGO
The World Cornea Congress highlights the international corneal community's endeavors in clinical and research areas. It is held every five years and is sponsored by the Cornea Society. The three-day meeting will include both invited speakers and a call for papers, as well as a poster session each day and an exhibit hall. The Congress will immediately precede the American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators Symposium and Congress. For more information, visit corneasociety.org.

17 - 21
SAN DIEGO
The American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators' annual Symposium and Congress will take place in San Diego at the San Diego Convention Center. The ASCRS Annual Symposium is the largest U.S. meeting dedicated exclusively to the needs of the anterior segment specialist. The simultaneous ASOA Annual Congress is the leading practice management program for comprehensive ophthalmology and subspecialties. The meeting will be preceded by a glaucoma subspecialty day covering critical updates, robust debates and interactive case studies on what comprehensive ophthalmologists and anterior segment surgeons need to know about glaucoma management. CME hours will be available. For more information, visit annualmeeting.ascrs.org.

MAY

3- 7
DENVER
The theme of the Association for Research in Vision and Ophthalmology 2015 Annual Meeting is "Powerful Connections: Vision Research and Online Networking." Online networking is changing the way people communicate, collaborate and conduct research. ARVO 2015 will explore the increasing importance of these networks in exchanging ideas, promoting scientific discourse, sharing discoveries, building global collaborations and advancing careers. The ARVO Annual Meeting is the largest gathering of eye and vision researchers in the world, attracting more than 11,000 attendees from more than 75 countries; approximately 45 percent of attendees are from outside the United States. The Annual Meeting features five days of innovative and cutting-edge vision science and eight major lectures, including an opening and a closing keynote. CME is available. For more information, visit arvo.org.

JUNE

6- 9
VIENNA, AUSTRIA
The European Congress of Ophthalmology, in conjunction with the American Academy of Ophthalmology and the Asia-Pacific Academy of Ophthalmology, will convene its next congress in Vienna the birthplace of modern European ophthalmology. Over 150 countries will be represented at the Congress, and cutting-edge topics, including retinal pigment cell transplantation, will be discussed. The official language of the Congress is English, and no simultaneous translation will be provided. CME hours will also be available. For more information, visit soe2015.org.

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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; cardiogenic shock; 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; while administered topically, it can be absorbed systemically and systemic adverse reactions to beta-blockers may occur (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported).

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 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.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: (continued)

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

Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Beta-blockers 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 diabetics (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients who may develop thyrotoxicosis to avoid abrupt withdrawal of beta-blockers 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-blockers due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-blockers 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: Use caution in the co-administration of COMBIGAN® with: antihypertensives or cardiac glycosides; beta-blockers (concomitant use of two topical beta-blockers is not recommended); calcium antagonists (avoid co-administration in patients with impaired cardiac function); catecholamine-depleting drugs; CNS depressants /anesthetics; digitalis and calcium antagonists; CYP2D6 inhibitors; tricyclic antidepressants; and monoamine oxidase inhibitors.

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

[a]Includes preferred, approved, and tiers 1-4, with and without step-edits, and also includes prior authorization, based on 203,671,234 total lives.

1. Managed Markets Insight & Technology, LLC, database as of December 2013.

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COMBIGAN®

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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.

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Recent Advances in Vitreoretinal Surgery

A look at the improvements in instrumentation and technologies that are reducing surgical risks and improving visual outcomes.

Michael McClintock, MD, and Kourous Rezaei, MD, Chicago

New advances in transconjunctival pars plana vitrectomy systems have provided many potential benefits to patients and surgeons. These include decreased conjunctival scarring and incidence of dry eyes post-surgery; more efficient surgery; decreased postoperative inflammation leading to less pain and more patient comfort; improved cosmetic appearance following surgery; decreased astigmatic changes; and quicker visual recovery. This article reviews some of the prominent recent advances in vitrectomy surgery.

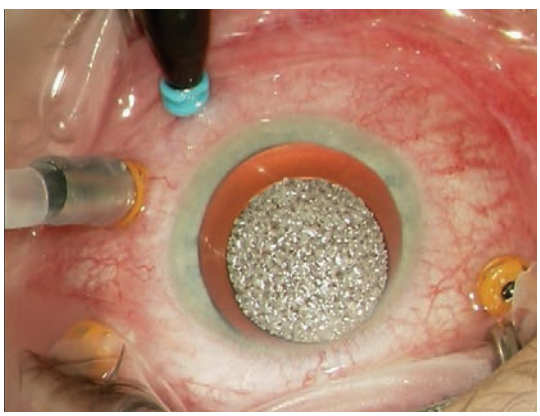

Figure 1. Location of valved trochars and chandelier light during vitrectomy surgery.

Size and Design Advances

Modern systems utilize various gauges including 23 ga., 25 ga. and 27 ga., and are available as a trocar/cannula system. Advances have been made with better instrumentation and wound-construction techniques to minimize the risk of wound leakage, hypotony, and endophthalmitis. Sclerotomy wound construction techniques involve trocar entry made at an oblique angle to lengthen the wound and maximize the chance of spontaneous closure. The trocars themselves have been redesigned to result in easier insertion and smaller wound profiles that are more likely to self-seal. If there is evidence of leakage at the conclusion of surgery one should suture the leaking sclerotomy to minimize postop complications.

A relatively new addition to the trocar system is the addition of valves, which allow vitrectomy surgery in a closed system, minimizing leakage of fluid during instrument exchange, reducing the potential for vitreous/retina incarceration and minimizing intraoperative intraocular pressure fluctuations. The latter may decrease the risk of hemorrhage during diabetic dissection; prevent hypotony during vitrectomy surgery, avoiding suprachoroidal hemorrhage and reducing the flow of fluid during surgery; and minimize turbulence (i.e., having fish eggs during perfluoron injection). It is important to note that when extra fluid such as perfluoron or silicone oil is injected into the eye while valved trocars are used, a drainage mechanism (i.e., vent or suction with cutter/soft-tip cannula) must be provided to avoid increased intraocular pressure and optic nerve/retina hypo-perfusion during surgery.

Cutter design itself has been revised to improve its surgical utility. Larger port areas have been employed to hasten vitreous removal. Further, the port itself has been migrated closer to the tip of the cutter, enhancing stability when cutting near mobile retina and in many cases allowing it to be used as a dissecting instrument, as well.

Cutter speed has also been increased through different mechanisms. Higher cut rates reduce the size of each in-

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dividual "bite" of vitreous, which in turn decreases the cutter-induced vitreoretinal traction during vitrectomy. This may be important during maneuvers such as removal of vitreous near a detached retina, minimizing the risk of iatrogenic retinal breaks.

Duty cycle is another variable that can be adjusted by the surgeon during the vitrectomy surgery, independent of the cut rate. It refers to the percentage of time the cutter port remains open during each cutting cycle, and the surgeon may choose between open or closed bias. When operating at close proximity to the retina, the closed bias decreases the likelihood of tissue incarceration, that is during peripheral vitreous shaving or fibrous tissue dissection. On the other hand, the open biased mode would allow a greater flow of fluid, such as during core vitrectomy without needing to change the cut rate.

In the future, smaller instruments such as 27-ga. trocar systems that provide superior fluidics and minimize surgical trauma will likely become more widely adopted. Such systems further reduce the the need for suturing; reduce surgical trauma; improve postop recovery; and lead to faster visual recovery. Further, in complex surgical cases, small cutters may allow surgeons to reach areas that would have been difficult to access with larger instrumentation.

Better Visualization

Visualization during vitrectomy surgery has significantly improved over recent years. The two main components that contribute to this improvement are better viewing systems and improved lighting.

Newer non-contact wide-angle viewing systems have optics similar to indirect ophthalmoscopy. The panoramic view offers more than 100 degrees of field of view, allowing the visualization of peripheral retina and vitreous with minimal need to rotate or tilt the eye during vitrectomy surgery.

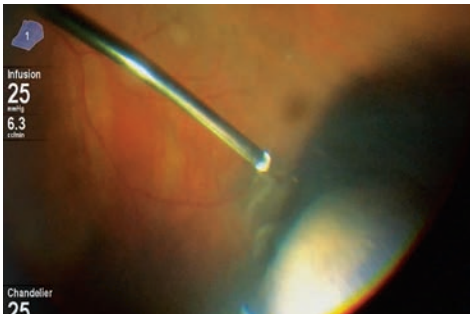

Figure 2. Scleral depressed endolaser treatment in aphakic patient. Perfluoron is placed over the posterior pole.

To view video of the two procedures depicted in this article, visit http://tinyurl.com/25GTrochar and http://tinyurl.com/25GSDPPV.

Higher lumen light sources have been developed to compensate for the lower amount of light transmitted through smaller-gauge instruments. These sources are more powerful and can be combined with special filters to minimize the risk of retinal phototoxicity from shorter wavelength light. Furthermore, chandelier light systems have freed up the hands of surgeons, allowing them to perform peripheral vitreous shaving without the need of an assistant, and bimanual dissection techniques in complex diabetic or proliferative vitreoretinopathy patients. It is important to be aware of the potential for phototoxicity and to reduce retinal light exposure to the minimum needed.

Illumination will continue to improve with the use of brighter illuminators, with possible directional and smaller-gauge chandelier lights. Further, chandelier lights could be repositioned easily to illuminate different locations of the globe. On the other hand, better small-gauge illuminating instruments may one day obviate the need for chandelier lights altogether.

The most revolutionary change in the future will probably be the use of optical coherence tomography during vitrectomy surgery. In much the same way that OCT revolutionized our clinical practice in the office, it will probably also revolutionize retinal surgery. The current state of technology for intraoperative use is at an early stage, similar to the time when OCT first became available for office use. Down the road, intraoperative OCT will probably look very different.

Another potentially revolutionary change would be the application of smart technology in the operating room. It would have an impact on every aspect of the surgery, from the time the surgery is scheduled, to the moment patient enters the operating suit (or the hospital) until the moment the patient leaves. Electronic health records are only a small part of this communication pathway. Much of the equipment and devices used for patient care during surgery would be able to communicate to make surgery safer and more efficient. Finally, instrument quality will continue to improve. This includes increasing the rigidity of small-gauge instruments to prevent bending or breakage during vitrectomy, especially when operating in the peripheral retina. REVIEW

Dr. McClintock is the senior fellow in vitreoretinal surgery at the Rush University Medical Center and Illinois Retina Associates in Chicago. Dr. Rezaei is an associate professor of ophthalmology at Rush University Medical Center and senior partner at Illinois Retina Associates. Contact Dr. Rezaei at Illinois Retina Associates, 71 W. 156th St., Ste. 400, Harvey, IL 60426. Phone: (708) 596-8710; fax: (708) 596-9820; email: karezaei@yahoo.com.

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(continued on page 73)

Two Decades In Translation

For 20 years, "Therapeutic Topics" has explored ocular disease. Here's an update on where translational medicine stands today.

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

Recently, there's been a flurry of discussions in the biomedical airwaves about the status of programs in translational medicine training and development. This comes as we approach the 10-year mark of the first efforts to train translational scientists.[1,2] Way back in 2006, the National Institutes of Health decided it was time to provide tangible resources for a relatively new concept called translational research, and so it created the Clinical and Translational Science Awards program. Its goal was to provide more direct means to support the application of basic science to questions of human disease and public health. By providing financial support, the CTSA helps to focus the view of many basic scientists, pushing them to think of the potential clinical applications of their work.

While many have adopted the phrase "bench-to-bedside research" as a pseudonym for translational science, few projects ever begin *de novo* with the aim of spanning that entire distance. And while recruiting basic scientists to pursue more clinically relevant projects is key, attracting clinicians to projects that integrate basic science with therapeutic development and application is just as important.[3] It strikes us that we've been doing just this for some time, and it's this intersection of science and medicine that has formed the basis for 250 installments of "Therapeutic Topics" over the past 20 years *(see "The Roots of Translation," on the opposite page)*.

This month, we consider one example of applying a translational approach, and describe how we have followed a continuous thread of experimental questions and answers focused on blinking and its relationship to ocular surface disease. We discuss how this knowledge has advanced clinical thinking and refine endpoints in clinical trials. This retrospective describes a 40-year mission based on simply following the physiology with a dogged determination that reminds us of a line from Tennyson's *Ulysses*: "To follow knowledge like a sinking star, beyond the utmost bound of human thought."

Blink Biology in the Clinic

The process of reflex and conscious blinking has always been understood to be an essential element of visual function, but most research prior to the past few decades was focused on psychological and behavioral aspects of blinking.

One of our first observations on blink made in the clinic was noting that superficial punctate keratitis was often located in the inferior crescent of the palpebral fissure.[4] Following up on this, we videotaped 10 patients and 10 controls, and found in subjects with keratopathy a consistent pattern of incomplete blinking that left this exposed region of the cornea scattered with puncta. While both groups showed a similar blink rate (16 to 17 blinks/min.), blinks were complete (where the upper lid makes contact with the lower lid) in 80 percent of the normal group, and in only 7.5 percent in patients with SPK. This suggested that the ocular surface pathology, SPK in this instance, was secondary to a primary blink abnormality rather than the keratitis modifying blink secondarily. This modest clinical finding of 1976 became the starting point for a thread that has woven through our research as it made its way into the lab, out to the clinic and back again several times over.[5-13]

Tear-film stability is a natural focal point for researchers interested in dry eye. Tear-film breakup time is a metric

This article has no commercial sponsorship.

used clinically and experimentally, and yet was decidedly in need of revisiting. We found that with a small, precise quantity of fluorescein,[5-7] the TFBUT threshold for dry eye was recalibrated at seven instead of 10 seconds. Why would this small change be of any significance? The answer lay in the blink. If tear-film breakup occurs at 10 seconds, and blink rate is at 6 seconds, then all is well; the ocular surface stays lubricated. However, when TFBUT and blink rate approach each other, then timing becomes critical as the reserve time or buffer zone narrows.

Recognition of the intricate nature of these two metrics led to the development of the ocular protection index.[8] The ratio of tear-film breakup time to another metric, inter-blink interval, provides an instantaneous snapshot of ocular surface health. When patients have OPI scores less than 1, i.e., TFBUT is less than IBI, the ocular surface is exposed. When patients have OPI scores greater than 1, i.e., TFBUT is greater than IBI, the tear film remains stable between blinks, and the ocular surface remains protected and comfortable. The goal of developing metrics such as OPI is to allow for a precise, reproducible measure of dry eye that might be modifiable with treatment. While there are many factors contributing to the dry-eye phenotype (such as age, environment, medications and visual activity), all of these converge on the tear film and its primary homeostatic regulator, the blink.

Our attention to staining as a precise endpoint resulted in using a yellow low-pass filter at the slit lamp. This filter bumps up the scoring of SPK by a whole grade, a heightened sensitivity that has multiple implications, both to the practicing clinician and to the translational researcher grading dry-eye subjects. Firstly, normals might all have staining if you look close enough; secondly, the filter can provide a tipping point for both false positive and false negative diagnoses of dry eye; and thirdly, total clearing of staining is not physiological. We have continued to improve on staining assessments by adding automated analysis of images for systematic grading of punctate keratitis on a numerical scale, and our article on the subject has been accepted for publication in a 2015 issue of *Investigative Ophthalmology and Visual Science*. This system provides an extremely consistent output of data, particularly across multi-centered studies that might involve as many as 30 sites.

Automating Blink Analysis

Our most recent work on blink telemetry involves automated, continuous monitoring of the blink throughout the day, to further dissect patterns of blink behavior in normal and dry-eye subjects.[11-13] One observation from these studies is that dry-eye patients have prolonged blink closure times, more than six times longer than normal subjects, a phenomenon similar to the micro-sleeps described in the literature on fatigue.[13] These extended blinks result in dry-eye subjects having their eyes closed five times longer per minute than a normal subject.[11] A number of reports have shown that the closed-eye tear film has a higher relative amount of inflammatory cells and IgA, suggesting a cleanup or surface maintenance function during sleep.[14,15]

The Roots of Translation

Thirty years ago, the pharmaceutical industry interacted in a very limited capacity with physicians, including ophthalmologists. Today, this standard has radically changed, with ophthalmologists taking part in everything from clinical study design to interacting with the Food and Drug Administration on drug development programs every step of the way. These translational researchers are now intimately involved in bringing the drug and the disease more closely together, and have a unique set of skills to thank for their success.

Translational researchers have the ability to recognize scientific advancements that have application in the real world of treating disease. They act as a bridge, bringing the clinical problem back to the lab, and the laboratory finding out to the clinic. Trained in disease diagnosis and management, epidemiology, laboratory skills and data analysis, translational researchers recognize which preclinical advancements—such as a biomarker or assay—can be developed into new diagnostics. The capacity to understand advancements in the parallel universes of basic science and clinical therapeutics puts the translational researcher at the productive interface where they intersect, acting as an interpreter to each. In these times of shrinking funding, these researchers integrate a kind of pragmatism into science, pruning unnecessary esotericism from the laboratory, while also providing the nascent spark for many start-up and publically traded companies when following an idea or new discovery.

This column's editor, Mark Abelson, MD, was one of the first ophthalmologists to see the value of translational research, an instinct he honed early in his educational career. A product of the cornea research fellowship track at Harvard Medical School, Mark Abelson's clinical acumen was shaped almost 40 years ago by his mentors, Claes Dohlman, MD, PhD, and Mathea Allansmith, MD. Mark first began lending his clinical experience to pharmaceutical development in 1976. Since that time, he has been central to the development and approval of more than 30 new drugs. His singular vision and no-nonsense problem solving approach provided the building blocks that evolved into the clinical research organization, Ora Inc., 30 years ago. Today, Ora's scope and breadth weave clinical and preclinical research into the tapestry of translational science. Mark's career has spanned 40 years of clinical practice, drug development and, most importantly, the education of future translational researchers.

With this issue, we celebrate Mark's 250th consecutive Therapeutic Topics column—which most often focuses on areas of translational clinical research—and we look forward to many more.

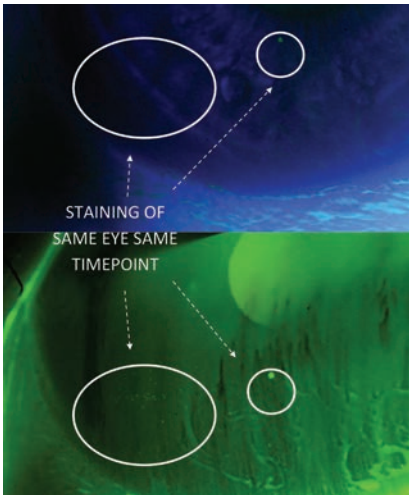
—The Editors

It's possible that these subconscious closures are a related compensatory mechanism.

The finding that dry-eye subjects blink more, blink longer and spend a great deal of time with eyes closed leads to one of our recent passions: visual function. We know that aside from pain and discomfort, visual function is what patients care about, what drives quality of life and what clinicians are trying to preserve. One of our first endeavors into visual function was with a metric that directly related to blink: the inter-blink interval visual acuity decay, or IVAD.[9] This computerized assessment of visual acuity dynamics under conditions of ocular surface stress measures a loss of acuity or blurring during a visual task performed within one blink interval. This metric is used particularly after exposure to a controlled adverse environment, a disease model in which the dry-eye subject's ocular signs and symptoms are brought to a highly exacerbated state.[10]

One of our first efforts in evaluating therapeutics with the CAE investigated the activity of a topical formulation of ecabat sodium. This compound had no effect except that it normalized blink rate, reducing it by half. This finding led us to the realization that drugs with potential for treating dry eye would have to positively affect blink rate, and that this was a sensitive indicator of therapeutic benefit, as well as an early protective mechanism. Furthermore, halving blink rate seemed significant to visual function and conversely, doubling blink rate to maintain tear-film stability, seemed to be the catch-22 linking blink to fatigue, and brought us back to the literature on fatigue, alertness and blink as an indicator of both.[16]

Other more subtle and realistic assessments of visual function are needed to understand how dry eye is affecting the life of the patient. We have recently been analyzing this through the study of reading—both short and long passages as well as reading silently and out loud—in an effort to move this qualitative measure forward into clinical trials as a quantitative, real-time measure of one of the most important patient activities. We also study reading rates in the context of blinking, and have found that, in studying either blink or reading, the crucial element is an understanding of the physiology that allows us to devise accurate, reproducible metrics that yield clinically meaningful measures.



Corneal fluorescein staining with (bottom) and without (top) a low pass filter. Clinicians typically view an unfiltered image, so the resolution is reduced when compared to an image with filtration. When using these higher resolution optics it's not unusual for control patients to exhibit low but detectable levels of corneal staining.

Assessment of symptoms is of critical importance and highly difficult due to their subjective nature. We discovered while carrying out blink telemetry studies that dry-eye subjects have lower blink rates during times of fewer symptoms, suggesting that blink data might be a useful surrogate to corroborate dry-eye symptom measures. Thus, blink links not only to tear-film stability but also to symptoms, and could provide corroboration for the often less-than-reliable data collected from subjects in diaries. Nevertheless, validating diary data in a clinical trial of highly symptomatic diseases such as allergy and dry eye remains critical, and we have been working with IT to produce cell phone app diaries as well as hardware that allow subjects to monitor and image ocular redness and symptoms on their own in real time. These images are uploaded to an automatic system of redness grading that has been shown to highly agree with clinical grading.[17] Automation is the future of clinical trials, and we're working hard to develop software systems that automate grading of redness as we did staining, to minimize investigator subjectivity and tighten the dataset.

The CAE has proven invaluable in our understanding of dry eye. The array of exogenous and endogenous variables that impact dry eye partly explains why development of effective dry-eye therapies has been so problematic. By exposing dry-eye subjects to a hot, dry and ventilated environment, and providing them with a continuous visual task, baseline conditions of dry eye are exacerbated in equal measure in the entire cohort. This model constructs a stable, heightened baseline for a population that otherwise would be highly variable in their natural state. From this platform, the effect of modifications in environment or addition of a therapeutic is more readily visible.[10,18,19]

We use the CAE model to inform our study designs and refine our understanding of disease subtypes. Screening with the CAE was used to identify modifiable patients in Phase III studies of MIM-D3 and Lifitegrast,[20,21] and served to help establish the relationship between dry eye and allergy.[22] Models such as the CAE can be invaluable tools to actually identify which patients might respond to a specific therapeutic: subgroups that might be more sensitive to a mucogenic, an anti-inflammatory or a tear substitute tailored to relieve symptoms. We have used the CAE to test contact lens tolerability, a practical outcome that provides information for both patient and clinician. The CAE has also been used to aid in the development of tear substitutes such as

Systane (Alcon Laboratories).

It is readily apparent from this example of a seemingly arcane physiological phenomenon such as blink that one clinical observation can lead to a generation of translational research. From the clinic to the lab, the knowledge gained from the physiology of blink has led to numerous byroads that young researchers might follow. Likewise, when new compounds are conceived, it is translational exploration that brings these breakthrough discoveries from test tube to treatment. Allowing for this progress are advances in translational research like those we've discussed here, as well as those we've left for later columns, such as drug formulation and safety issues.

Translational medicine may streamline the plodding stepwise process typical of therapeutic development, but in the end all must face the gauntlet of clinical assessment, and we're all part of the translating process. REVIEW

Dr. Abelson is a trustee of the Schepens Eye Research Institute, emeritus surgeon of the Massachusetts Eye and Ear Infirmary, and a clinical professor of ophthalmology at Harvard Medical School. Ms. Smith and Dr. McLaughlin are medical writers at Ora Inc.

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Preserving Vision in Neovascular Glaucoma

To effectively manage this disease, be sure to address the underlying causes, not just the elevated pressure.

Agnes Huang, MD, Seattle

Neovascular glaucoma is a secondary glaucoma usually associated with severe retinal hypoxia. Most eyes suffering from this condition have ischemic changes, although about 3 percent of cases are associated with inflammation without ischemia.[1] How we treat these patients depends on the cause of the ischemia, the stage of the disease and the individual's visual potential.

Potential causes of neovascular glaucoma include diabetic retinopathy; central retinal vein occlusion; branch retinal vein occlusion; ocular ischemic syndrome; tumors; chronic inflammation; chronic retinal detachment; and radiation retinopathy. (The most common causes are diabetes, CRVO and BRVO.) Retinal ischemia triggers the release of vasoproliferative factors, including vascular endothelial growth factor, fibroblast growth factor and interleukin-6. VEGF promotes the formation of fenestrations in new, immature vessels, allowing vascular hyperpermeability and increasing the level of inflammatory mediators in the eye; this may cause pain, independent of intraocular pressure.

As vasoproliferative factors diffuse anteriorly from the retina to the anterior segment, fibrovascular proliferation in the angle causes obstruction of the trabecular meshwork and progressive synechial closure of the angle. The inevitable rise in IOP leads to neovascular glaucoma.

Because the impact of the disease evolves over time, it's important to stage the disease when you encounter it. In stage 1, neovascularization occurs on the iris. You'll see tufts of vessels on the anterior iris, usually at the pupillary margin. (Note: These may be difficult to see in dark irides.) Because the angle is unaffected, the IOP is normal at this stage of the disease. In stage 2, secondary glaucoma develops. Abnormal blood vessels now extend to the angle, causing fibroblastic membranes to form there, blocking the trabecular meshwork—but without synechial closure. At this stage the angle still appears to be open, but intraocular pressure begins to rise. (Unfortunately, it tends to remain elevated, even if you achieve regression of the neovascularization.) Stage 3 is marked by secondary angle-closure glaucoma. The myofibroblasts formed by the abnormal blood vessels contract, leading to synechial closure of the angle and elevated IOP.

Key Factors to Address

When managing a patient with neovascular glaucoma you need to address at least four things that will affect whether the patient retains or loses vision: the presence of abnormal blood vessels; excessive VEGF factor inside the eye; inflammation; and (depending on the stage of the disease) elevated intraocular pressure. How you address these should depend, at least in part, on the stage of the disease when you encounter it.

• ***Regression of abnormal blood vessels.*** To address this part of the disease we inject intravitreal anti-VEGF therapy, usually bevacizumab (Avastin) or ranibizumab (Lucentis), although aflibercept (Eylea) and pegaptanib (Macugen) are also available. The neovascular growth will not disappear, but it will collapse within a few days to a week after injection as a result of diminished vascular permeability. The anti-VEGF agents also help by decreasing the

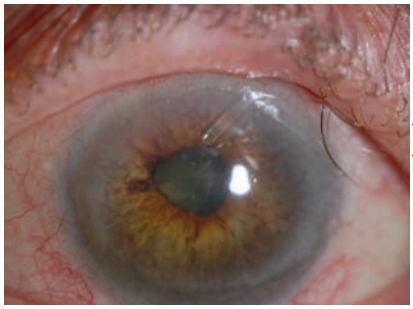
pain associated with the inflammation that accompanies the disease, independent of making the blood vessels go away. (Unfortunately, these drugs only have a transient impact, so repeat injections may be necessary.)

These drugs are usually injected into the vitreous, although some surgeons have tried putting them into the anterior chamber angle as well, hoping to cause regression of the vessels blocking the angle. If the angle is not closed, this might allow the pressure to drop somewhat. However, most surgeons just place the drug intravitreally because these eyes usually have retinal ischemia.

• ***Addressing the ischemic drive to neovascularization and reducing inflammation.*** The former is best addressed via retinal ablation, whether it's panretinal photocoagulation or cyclocryoablation. This will produce a sustained reduction of the ischemic drive that produces the vasoproliferative factors, along with a reduction in the amount of VEGF-producing tissue. Topical corticosteroids can be used to reduce inflammation.

• ***Lowering the elevated pressure.*** When treating neovascular glaucoma you also have to treat the elevated IOP. You can do this using medical therapy, including beta blockers, topical or oral carbonic anhydrase inhibitors, alpha-adrenergics or prostaglandin analogues. The prostaglandin analogues are equivocal because they can be pro-inflammatory, but they're often used anyway, trying to prevent a bad situation from becoming worse. Atropine increases uveoscleral outflow and diminishes congestion, helping make the patient more comfortable. You should avoid anticholinergics such as pilocarpine because they can potentiate inflammation.

You can also do surgery to treat the high pressure. One option is trabeculectomy, although it's important to note that your results will be much better if you use antimetabolites. At 12 months, in various studies, 66 percent of neovascular glaucoma patients were controlled after trabeculectomy with antimetabolites while only 20 percent were controlled without antimetabolites. Overall, the success rate tends to be poor with trabeculectomy because of the risk of inflammation and the presence of abnormal blood vessels. (Other factors that increase the risk of failure in this situation include being younger than 50 years old, having had a previous vitrectomy, cataract surgery or retinal detachment, and having a lot of blood inside the eye.) There's no question that a neovascular glaucoma patient undergoing trabeculectomy will do better if the eye has controlled inflammation and neovascularization.



Peter A. Netland, MD, PhD

An 84-year-old man with neovascular glaucoma after central retinal vein occlusion, with an Ahmed Glaucoma Valve.

Another surgical option is to implant a seton, or tube shunt. Many surgeons choose this over trabeculectomy because it's less affected by inflammation, which can cause closure of the trabeculectomy. Setons control IOP in 60 to 89 percent of these patients for the first year; however, the success rate diminishes to 10 to 46 percent at five years. (The type of tube used—e.g., Molteno, Baerveldt or Ahmed—doesn't seem to affect the success rate.[2])

The question then becomes, which surgery is best for treating neovascular glaucoma? The Tube vs. Trab study excluded patients with neovascular glaucoma; however the literature in general suggests that trabeculectomy is less likely to be successful, simply because inflammation is such a big factor in this disease.

This is even more important if the need to reduce pressure is urgent. I recently treated a patient who came in with neovascular glaucoma and a pressure of 70 mmHg. The eye was painful. In that situation, I couldn't afford to wait until the abnormal blood vessels and inflammation had subsided. I had to address all concerns at the same time, so I chose a tube shunt rather than trabeculectomy. If you do have time to address the inflammation, then either surgery may be effective; if not, it makes the most sense to implant a tube shunt.

Staging and Visual Potential

The most effective treatment for neovascular glaucoma at any given point in time depends on the stage of the disease and the patient's visual potential. The key thing to remember is the importance of treating the underlying disease.

If the patient is in stage 1—pre-glaucoma with abnormal blood vessels in the pupillary margin—you want to eliminate the neovascularization before the pressure goes up. Usually, that's when you inject anti-VEGF drugs intravitreally. (Some surgeons have described cases in which they chose subconjunctival injection of bevacizumab, but most surgeons inject intravitreally.) You may want to do panretinal photocoagulation if there's a lot of retinal ischemia. You can do goniophotocoagulation if you're just trying to get rid of the abnormal blood vessels in the angle. You can also treat any inflammation that is present.

If the patient is at stage 2, the angle is open but the pressure is elevated because of all the abnormal blood vessels in the angle. In this situation

you should do PRP and inject an anti-VEGF drug to decrease pain and complications. To address the elevated IOP you should provide one of the standard glaucoma treatments, whether it be in the form of eye drops or orally, and go on to glaucoma surgery if drugs can't control the IOP.

By the time the patient gets to stage 3, where the angle is closed and IOP is elevated, you have to address all of these issues. So you want to do PRP, inject an anti-VEGF drug, reduce the inflammation and treat with glaucoma drugs and/or surgery. Usually, a glaucoma drainage implant is needed once the disease has progressed this far. In really bad cases, if the patient has very poor visual potential, you can use a cyclodestructive procedure to destroy the ciliary body. This helps to control the pressure in anywhere from 40 to 70 percent of these patients, but a lot of patients will end up with hypotony; phthisis is likely to occur in 2 percent of cases; and 22 percent will lose vision altogether. (Note: If you're going to do a cyclodestructive procedure, whether it be laser or cryotherapy, preop treatment with an anti-VEGF drug will decrease the risk of a poor outcome.)

How aggressive you want to be when treating a patient with neovascular glaucoma depends on the level of vision the patient has. If the patient still has vision, you want to preserve it. So generally, you want to do the PRP and anti-VEGF to diminish vessel formation, and you want to do a trabeculectomy or implant a glaucoma drainage device to decrease IOP. If the patient's vision isn't good, but he's not a good surgical candidate—perhaps a frail diabetic or someone on dialysis—you can do laser photocoagulation. If vision is limited, you can consider doing transcleral cyclophotocoagulation. If there's absolutely no visual potential, at that point you go to comfort care. If the IOP is likely to remain high, you can make sure the patient won't have pain as a result. You can use a retrobulbar injection to kill off the pain fibers in the optic nerve, or do enucleation or evisceration. At that point your job becomes to keep the eye comfortable.

Getting to the Cause

The most common mistake I've seen doctors make is not treating the cause of the problem. I've had patients whose previous doctor was focused on treating the elevated pressure, thinking he could address the neovascularization later. To preserve vision, it's really important to start treating the cause of the neovascularization immediately, whether you treat with an anti-VEGF drug or with PRP. Especially if you're planning to do glaucoma surgery, having neovascularization and inflammation will only make the surgery more difficult, and the outcome is more likely to be poor.

Even giving an anti-VEGF injection one day before surgery can make a huge difference; you'll start seeing vessel regression within a day or two. Even if you catch the disease at stage 1, your results will be far better if you can cause the abnormal blood vessels to regress and eliminate the source of the VEGF, as well as any inflammation that's already present. (Although anti-VEGF drugs are very helpful in the early treatment of NVG, PRP is still helpful for achieving long-term regression of vessels.)

I think most doctors encountering these patients do realize the nature of the problem, but if the IOP is already very high—say 60 or 70 mmHg—they may feel that addressing that pressure is their first priority, and rush to do surgery. In some situations, that may be appropriate, but the reality is that this is not like acute angle closure, where the pressure abruptly soars over a very short period of time. These patients have had their pressure increasing slowly as the angle became crowded, and in many cases the patient isn't in much pain. In fact, when the pressure increases very slowly, it's impressive how high it can get without the patient having much discomfort. If the patient had acute angle closure glaucoma and a pressure of 70 mmHg, she'd be throwing up and complaining of the pain. If your patient isn't too uncomfortable, you and the patient may benefit from giving an anti-VEGF drug and other treatments a day or two to work before you perform surgery.

One other point: Some surgeons are concerned that an anti-VEGF injection may cause the IOP to rise a little bit. If you believe that's an issue, create a small paracentesis to allow removal of a bit of aqueous when you put in the drug. That will help prevent the pressure from rising too high and threatening the optic nerve.

It's Worth the Struggle

Unfortunately, even with IOP controlled, many studies have shown that anywhere from 3 to 48 percent of these patients will lose light perception.[3,4] So there's no question this is a tough condition to manage, especially in a profession in which so many of our patients have positive results. Nevertheless, appropriate treatment will indeed benefit these patients. Even though you won't always win the battle, a lot of vision will be preserved. REVIEW

Dr. Huang is the founder of Seattle Ophthalmology. She has no financial ties to any product mentioned.

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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.

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 (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.

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

ALPHAGAN® P

(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.

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Revised: 11/2012

Based on package insert 71816US15C

APC57BC13

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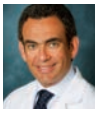
(brimonidine tartrate ophthalmic solution) 0.1%



New Filters for LASIK Screening

New studies with innovative indices are allowing surgeons to catch more risky corneas before surgery.

Walter Bethke, Managing Editor

When ectasia began to rear its ugly head several years ago in postop LASIK patients, surgeons scrambled for better ways to screen candidates who might be susceptible to this disastrous corneal thinning. Though vigilance and better screening methods have cut down ectasia rates, researchers are still hard at work developing even more precise ways to catch risky candidates. Here's a look at two new methods of LASIK screening that involve combining different methodologies in an effort to increase screening accuracy.

Clinical Data and Tomography

Brazilian ophthalmologist Renato Ambrosio and his co-workers have described their efforts at honing screening parameters in the past, including the development of the Belin-Ambrosio Deviation score, an index on the Oculus Pentacam that can help pick out suspicious corneas. The latest methodology they've been working on is called Enhanced Ectasia Susceptibility Screening; it combines clinical data with the Pentacam's tomography.

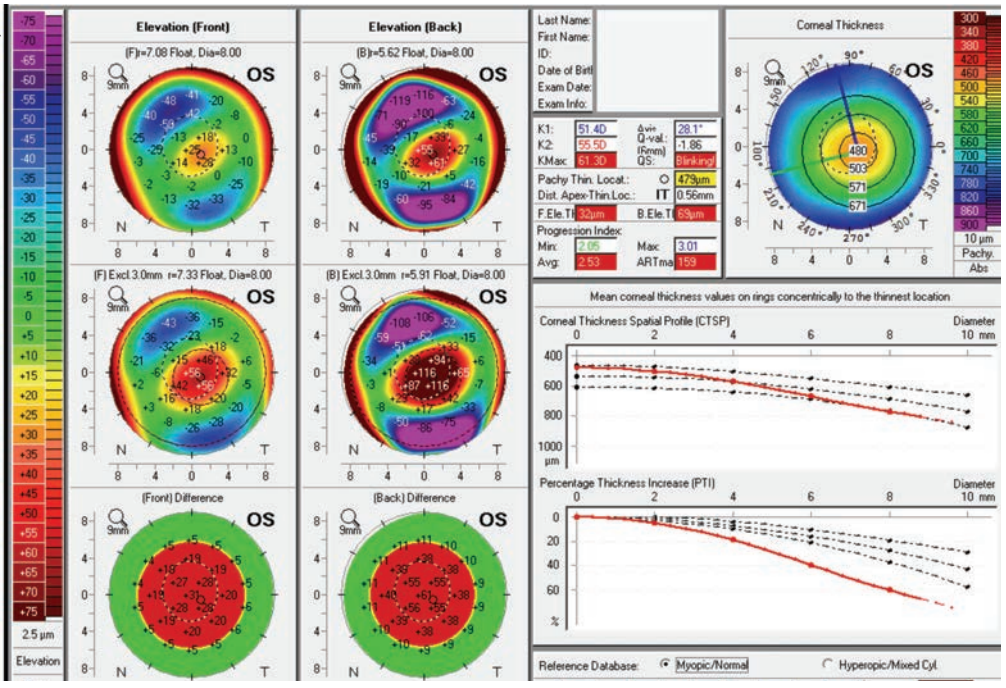
Dr. Ambrosio says the new screening method arose out of a need to catch the very subtle cases. "There's the question of what constitutes mild or forme fruste keratoconus in a susceptible cornea," he says. "In a study we did at our practice, we found we were still missing about 7 or 8 percent of cases—which is not good. However, we found that if we combine patient age and surgical parameters such as the percentage of tissue that's altered by the procedure, and perform a linear regression analysis using this data, our accuracy improves. We're also working on improvements in the final BAD score—or "D" value—in the Pentacam display. Today, the final D relies on the ablation, the thickness distribution and the highest curvature, or KMax. If you have a final D that's higher than 2.0, it's 99-percent sensitive in its ability to detect keratoconus."

To test the effectiveness of combining the clinical data (age, manifest refraction, spherical equivalent, maximum ablation and flap thickness) and the tomographic findings in screening patients, Dr. Ambrosio's group analyzed the preop clinical and tomographic data from 46 eyes of 38 patients who developed ectasia following LASIK procedures and from 266 control eyes of 141 patients who were stable after LASIK. The researchers found that the EESS using the combined parameters had a 90-percent sensitivity and 92-percent specificity, with an area-under-the-operator curve of 0.936 in terms of distinguishing between the groups (a result of 1.0 would indicate a perfect ability). Dr. Ambrosio says the method they used helped lend statistical weight to the findings. "When we did regression analysis, we tried to combine the factors to give a result that was a zero or a 1," he explains. "Everyone who was normal after LASIK would be zero, and everyone who was abnormal should be 1.

The University of Arizona's Michael Belin, MD, one of Dr. Ambrosio's collaborators, says a good analogy of how clinical factors impact treatment decisions is the erythrocyte sedimentation rate used to monitor inflammation. "A certain SED rate for a young patient would be highly suspicious, while the same SED rate in an older patient would be normal," he says. "In our classification system, if there was a final D value of 1.8 in a 21-year-old who desired LASIK, I probably wouldn't

This article has no commercial sponsorship.

Michael Belin, MD



The Pentacam's Belin-Ambrosio Deviation display, depicting advanced keratoconus. Significant abnormalities can be seen on both the anterior and posterior elevation maps, in the Kmax value, in the anterior and posterior elevation values at the thinnest point, in the Progression Index (avg.) and both pachymetric progression maps. The final BAD "D" value is more than 12 standard deviations from the norm, which is compatible with the clinical diagnosis of moderate keratoconus.

touch that patient. If that same value was in a 55-year-old patient, and given that there weren't any other abnormalities, that would probably be an acceptable number. We know younger patients are at greater risk, probably because the disease is progressive and, at a younger age, hasn't manifested itself yet. Similarly, if I saw a D value of 2—which would be a gray zone—and it was a middle-aged person with a low correction who was acceptable for surface ablation, that surgery would probably be acceptable in that case."

Dr. Ambrosio says the methodology behind the EESS is statistically powerful because it uses actual cases of postop ectasia. "The challenge in screening is that we know some normals may actually have very mild keratoconus and some keratoconus cases may be so mild they might be considered normal," he says. "Since we're aiming to detect with sensitivity and specificity the patients who will go on to have ectasia after surgery, actually using patients who had surgery and then did or did not develop ectasia is powerful. We're actually doing these studies based on a pool of ectasia cases that are sent to me. These cases are rare, especially ones that have the preop tomography data. In fact, any surgeons who have such cases in addition to the tomography data are welcome to send them. We need the files from the Pentacam to actually have all the data for analysis purposes, so we analyze each case in detail and calculate the BAD D value and develop future algorithms for the new regression analysis."

OCT and Topography

Jules Stein Eye Institute ophthalmologist Yaron Rabinowitz has found that bringing together optical coherence tomography with videokeratography (topography) helps paint a more complete picture of at-risk patients than just videokeratography alone.

Dr. Rabinowitz says he combined the technologies to fill in some gaps that may exist in corneal topographic screening. "I previously developed an index based on videokeratography called the inferior/superior dioptric asymmetry index, or I-S value," he says. "One of the criticisms of the I-S value is that videokeratography only looks at the anterior part of the cornea, not the posterior aspect." To help remedy this issue, he began to consider OCT as a complementary modality to topography. "OCT is good at measuring the thinning of the cornea," he notes. "This is helpful in screening because in keratoconus the cornea also thins in addition to becoming more asymmetric on topography. OCT also covers about 8mm of the cornea, and isn't limited to pachymetry in just the central or inferior region. So, if you want to have an index that will catch whether a cornea will eventually become keratoconic or a method that will help track keratoconus, you should follow both anterior surface changes and pachymetry, the latter of which involves the posterior surface. This gives you a three-dimensional look at the cornea."

The way Dr. Rabinowitz combines the technologies is to take the minimum pachymetry from OCT—i.e., the thinnest point—and combine it with the I-S value from the topography. Specifically, he divides the minimum pachymetry (PA) by four and multiplies the result by the I-S value.

(continued on page 73)

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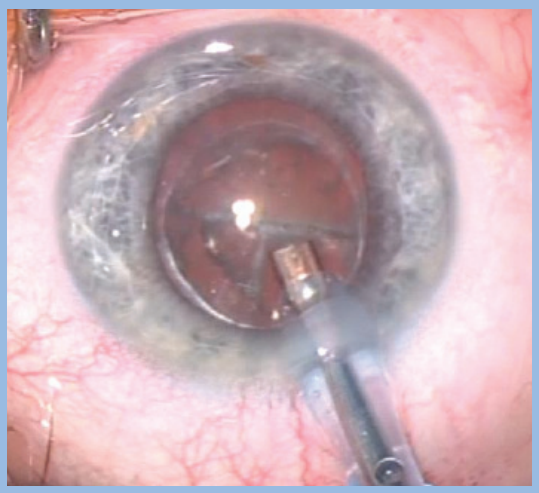

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Treating Postop PRK Pain with NSAIDs

Preoperative treatment of a topical non-steroidal anti-inflammatory in photorefractive keratectomy appears to function as a preemptive analgesia, according to researchers from the Saeyan Eye Institute in South Korea. Topical ketorolac and diclofenac showed similar potencies for pain prevention, but the duration of action appeared to be longer with diclofenac.

In a comparative case series, 94 patients were randomly assigned to two groups: ketorolac group (ketorolac 0.5% in one eye and ofloxacin 0.3% in the other eye); and diclofenac group (diclofenac 0.1% in one eye and ofloxacin 0.3% in the other eye). One drop of each ophthalmic drug was applied three times to each eye 30 minutes before PRK. No other NSAID or steroid was prescribed until four days after PRK. The patients were asked to score the postoperative pain in each eye with a visual analog scale at six, 18, 24, 36, 48, 72 and 96 hours.

The natural peak of pain was located between 24 and 36 hours. Initially, the degree of pain reduction was constant for both NSAIDs; it dropped after 24 hours in the ketorolac group and after 36 hours in the diclofenac group. The postoperative time-serial pattern of the pain score changed in the diclofenac group but not the ketorolac group compared with the pattern in the ofloxacin-treated eye. The visual outcome was not affected by either NSAID and significant complications were not noticed for a mean of seven months.

J Cataract Refract Surg 2014;40:1689-1696.
Hong J, Nam S, Im C, Yoon S, et al.

Intimate Partner Violence: Cause of Orbital Floor Fractures

In a retrospective chart review of facial fracture patients examined at the University of Iowa Hospitals and Clinics between January 1995 and April 2013, researchers found that intimate partner violence-associated assault was the third leading documented mechanism of injury in female orbital fracture patients. This translates into one of every 13 orbital floor fractures in female patients resulting from IPV-related assault.

A total of 1,354 women and 4,296 men sustained facial fractures during the time period reviewed. Of these, 405 women and 1,246 men sustained orbital floor fractures. The defined mechanisms of orbital floor fractures in women were, in order: motor vehicle collisions (29.9 percent); falls (24.7 percent); IPV-associated assault (7.6 percent); non-IPV-associated assault (7.2 percent). Among women with orbital fractures due to assault, leading patterns of injury included the following: isolated orbital floor fractures (12/31 IPV patients, 38.7 percent; 16/29 non-IPV patients, 55.2 percent); zygomaticomaxillary complex fractures (11/31 IPV patients, 35.5 percent; 5/29 non-IPV patients, 17.2 percent); and orbital floor plus medial wall fractures (5/31 IPV patients, 16.1 percent; 7/29 non-IPV patients, 24.1 percent). Involvement of ancillary services was documented in 20 percent (seven law enforcement and five social services agencies, 12/60) of assault-related orbital floor fracture cases. Ascertainment of patient safety was documented in 1.7 percent (1/60) of these cases.

Of note, 20.5 percent of the female orbital floor fracture patients in the study population had no etiology documented. Based on the underreported nature of IPV, it is probable that a substantial portion of these patients also sustained injury secondary to IPV that went unreported or undocumented. Given Iowa's relatively low rate of IPV prevalence (seventh lowest in the United States) these percentages are undoubtedly an underestimate for many sectors of the United States. Ophthalmologists treating orbital floor fracture patients should maintain a high index of suspicion for IPV and screen accordingly. Following IPV disclosure, patient safety should be assessed and referral provided.

Ophthal Plast Reconstr Surgery 2014;30:508-511.
Clark T, Renner L, Sobel R, Carter K, et al.

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REVIEW Advertising Index

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Scleral discoloration, irritation and decreased vision prompt a 66-year-old man to seek help from the Wills Eye Cornea Service.

Brenton Finklea, MD

Presentation

A 66-year-old male presented to the Wills Eye Hospital Cornea Service with a complaint of two years of worsening "dark spots" on his sclera and decreased vision in his left eye, along with chronic irritation and intermittent pain in both eyes.

Four years prior to presentation, the patient had undergone an "eye-whitening procedure" due to displeasure in the cosmetic appearance of his eyes, with a goal of correcting the chronic hyperemia and injection of the conjunctiva in both eyes. Over the past two years, he has required multiple additional procedures including Tutoplast graft and an amniotic membrane graft on the left eye. At the time of presentation to Wills Eye he was on prednisolone acetate 1% eye drops four times per day in the left eye.

Medical History

The patient's past medical history was significant for hypertension, asthma and a five-year smoking history. The patient had an ocular history of cataract extraction with intraocular lens implantation in both eyes in addition to the procedures previously discussed. Medications included aspirin, amlodipine, enalapril and a montelukast inhaler. Social history and family history were unremarkable. Allergies included penicillin G and neomycin.

Examination

The patient's uncorrected visual acuity was 20/20 in the right eye and 20/400 in the left eye, with pinhole improvement to 20/200. Pupils were equal, round and reactive to light, and confrontational visual fields were full to finger counting. Motility was full in both eyes. His intraocular pressure was measured at 16 and 9 mmHg in right and left eyes respectively. Mild blepharitis was present bilaterally. Anterior segment examination of the right eye revealed a calcified plaque with overlying epithelial defect nasally, and areas of absent conjunctival vessels. Remaining conjunctival vessels were engorged. The left eye contained large areas of scleral thinning with uveal show, absent conjunctival and scleral vessels, and a scleral patch graft overlying the nasal sclera. No epithelial defect was present in the left eye on presentation. Three exposed sutures were present around the scleral patch graft. Trace cell was seen in the anterior chamber of the left eye. Dense inferior superficial punctate keratopathy was found in both eyes, worse in the left. The remainder of the anterior and posterior segment examinations was significant only for multifocal posterior chamber intraocular lenses in both eyes.

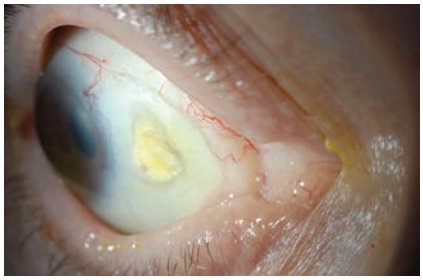

Figure 1. Slit-lamp photo of the right eye, showing a calcified scleral plaque with overlying epithelial defect nasally.

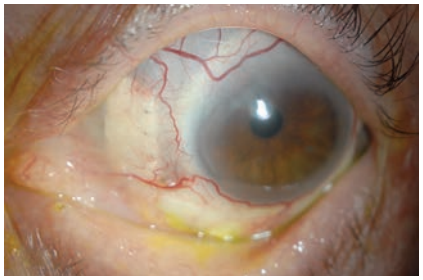

Figure 2. The left eye shows Tutoplast graft nasally with exposed sutures, with adjacent areas of scleral thinning.

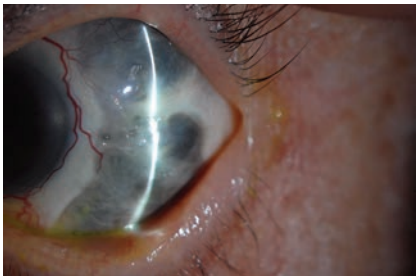

Figure 3. Slit-lamp photograph of the left eye showing severe scleral thinning temporally.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 68

Diagnosis, Workup and Treatment

Further investigation into the patient's ocular history found that he had undergone the I-Brite eye-whitening procedure four years prior to presentation. Examination showed extensive scleral thinning in the left eye which did not have an overtly inflammatory appearance, however the presence of cell and flare in the anterior chamber suggested an active inflammatory process. The history and examination pointed to a diagnosis of scleromalacia with active inflammation following the I-Brite procedure. Additionally, the progression of scleral thinning with active inflammation showed an incomplete response to topical steroid therapy.

The patient's topical steroid therapy was increased from four to six times per day in the left eye and aggressive lubrication was instituted in both eyes with artificial tears during the day and erythromycin ointment at night. Additionally, punctal plugs were placed into the lower eyelids bilaterally.

One region of sclera in the left eye had already been reinforced with a Tutoplast graft on presentation. The severe thinning of the temporal sclera made it likely that further grafting would be necessary if the patient continued to progress, however no further surgical intervention had been performed at the time of this publication.

In the presence of persistent intraocular inflammation and presumed active scleritis despite topical corticosteroid treatment, the patient was referred to the Uveitis Service at the Wills Eye Hospital for systemic workup of possible exacerbating conditions and consideration of systemic immunosuppression to further stabilize the eye.

Discussion

Eye-whitening procedures were pioneered in eastern Asia as a treatment for chronically hyperemic eyes, pingueculae and pigmentation. The basis of surgical eye-whitening technique involves extensive conjunctival resection (wide conjunctivectomy) and tenonectomy with topical mitomycin-C. Variations on the technique have included the use of bevacizumab injections.[1] Domestically, the I-Brite eye-whitening system is a proprietary version of these techniques employing conjunctivectomy and MMC. The subject matter has been a topic of much debate due to the concern for severe complications. While some papers have reported high patient satisfaction rates with low complication rates,[2] others have found complications in as many as 82.9 to 91.7 percent of patients, over half of which were considered to be "severe."[1,3,4] The most common complications include fibroproliferation (43.8 percent); dry eyes (32 percent); ocular hyperemia (30.9 percent); and intraocular pressure elevation (13 percent). Severe complications include scleral calcification (6.2 percent); scleromalacia (4.4 percent); diplopia (3.6 percent); strabismus (1.5 percent); and keratitis (1.2 percent), with scleral necrosis being present in 0.1 percent of cases.[1] Soolienah Rhiu and colleagues looked at incidence of scleral thinning, which was found to be as high as 43.8 percent. Additionally, persistent conjunctival epithelial defects were particularly common, found to be present in 45.8 percent of patients.[4]

It is often a relatively young population that seeks out these services, with recent studies showing average age ranging from 35.9 to 39.2 years old, with nearly two-thirds being female.[1,4] This young population is at particular risk as complications may be chronic and worsen with time, leading to a lifetime of treatment. It has been suggested that nearly one-third of patients require a reoperation due to complications of eye-whitening procedures, most commonly due to fibroproliferation following the initial surgery.[1]

Necrotizing scleritis without inflammation, also known as scleromalacia perforans, is most commonly associated with rheumatoid arthritis; however, there is a steady flow of cases showing scleromalacia following conjunctivectomy with MMC in the setting of pterygium surgery or eye-whitening procedures.[5,6] Individuals with a history of these procedures may not need to undergo the usual extensive laboratory and imaging workup for those with scleritis unless there is a history of prior systemic symptoms or suggestion of underlying rheumatologic disease. A thorough history prior to pursuing these procedures may help to decrease the incidence of postoperative complications in certain patients. Poor wound healing due to the use of MMC has been reported in individuals with acne rosacea, atopic keratoconjunctivitis, keratoconjunctivitis sicca, Sjögren's syndrome, blepharitis and herpes keratitis.[7]

Therapeutic options for necrotizing scleritis secondary to eye-whitening procedures or pterygium excisions with MMC focus on minimizing inflammation and severity of scleritis, while treating scleral thinning to minimize risk for globe perforation. Therapeutics for inflammation can include topical steroids but may also include systemic immunosuppressants such as oral corticosteroids, antimetabolites, immunomodulators or cytotoxic agents. Treatments for scleral thinning may include scleral patch graft, amniotic membrane graft, lamellar corneoscleral graft or conjunctival flaps to reinforce areas of reduced integrity.[8-10]

The high incidence of severe complications from cosmetic eye-whitening procedures such as I-Brite suggests that patients should likely be counseled against pursuing this procedure. Scrutiny of the procedure led the American Society of Cataract and Refractive Surgery to release a clinical alert warning providers about the risks associated with eye-whitening.[11] Additionally, due to the concerning outcomes of eye-whitening surgeries, the Korean Ministry of Health and Welfare banned the procedure in 2011. Despite these warnings the procedure continues to be advertised to patients domestically, and the American ophthalmology community will need to be prepared to treat complications as they arise.[12] REVIEW

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(continued from page 62)

"This gives what I call the PA/I-S value," he explains. "The lower the PA/I-S value, the greater the likelihood the patient has keratoconus. The higher the value, the greater the likelihood the cornea is normal. As a cutoff, anything less than 100 on the index is keratoconus and anything greater is normal."

In a study of the new index, Dr. Rabinowitz and his colleagues were able to identify 100 percent of early and forme fruste keratoconus as keratoconus, with seven normal patients being misclassified as abnormal (misclassification rate of 2.7 percent).[1] The researchers say the index helped reduce the misclassification rate of keratoconus suspects, a group they say is perennially hard to diagnose. When they only used the I-S value for the patients, they classified five keratoconus suspects as normal and 11 normals as keratoconus, for a misclassification rate of 7.8 percent. When they used the PA/I-S index, however, the misclassification rate shrunk to 4.4 percent.

Dr. Rabinowitz says the index has also proven useful for tracking treatments for corneal conditions. "It's also been helpful when tracking corneal collagen cross-linking," he says. "With cross-linking, you want to know if a patient's cornea is progressing—getting thinner or becoming more keratoconic—and using this index is a good way to track the progression or, conversely, to show that cross-linking is working because there is no progression based on the index." REVIEW

Drs. Ambrosio and Belin are consultants to Oculus.

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LUMIGAN® 0.01%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® (bimatoprost ophthalmic solution) 0.01% 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®** (bimatoprost ophthalmic solution) 0.01% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17.1)]*.

Eyelash Changes: LUMIGAN® 0.01% 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: Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% 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.

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 *[see Patient Counseling Information (17.3)]*.

Use with Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% 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 a 12-month clinical study with bimatoprost ophthalmic solutions 0.01%, the most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with **LUMIGAN®** 0.01% in this study included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

Postmarketing Experience: The following reaction has been identified during postmarketing use of **LUMIGAN®** 0.01% in clinical practice. Because it was reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** 0.01%, or a combination of these factors, includes headache.

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: 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®** (bimatoprost ophthalmic solution) 0.01% administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** 0.01% 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% 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®** 0.01% 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®** (bimatoprost ophthalmic solution) 0.01% 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/m^2 is at least 210 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.01% 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: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Also inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01%.

Potential for Eyelash Changes: Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01%. 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: Instruct patients 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: Advise patients 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%.

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

Use with Other Ophthalmic Drugs: Advise patients 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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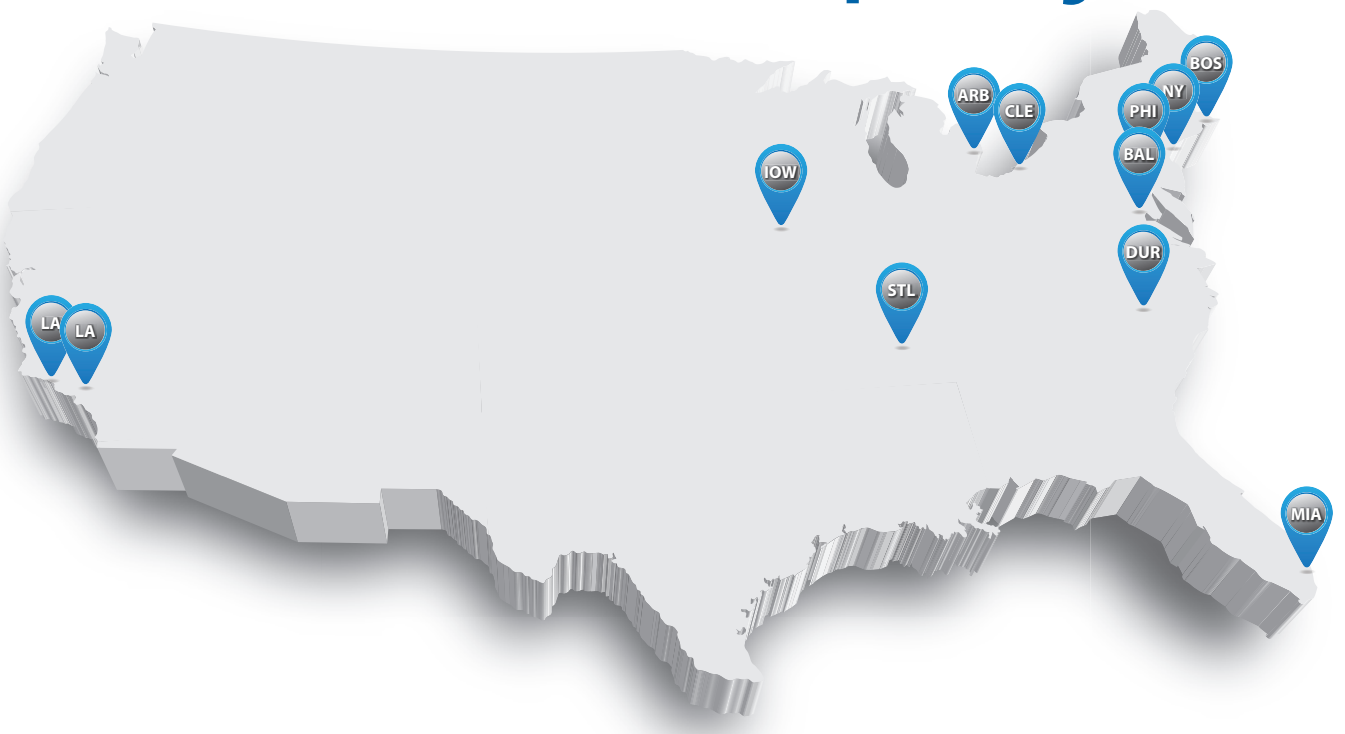

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INDICATION

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® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% 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.

Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. These products may also exacerbate inflammation, so use with caution in patients with active intraocular inflammation (e.g., uveitis). Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% 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. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

ADVERSE REACTIONS

The most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with LUMIGAN® 0.01% included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

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

1. LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol.* 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of October 2014.

LUMIGAN® 0.01%
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