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December 2014

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AMD=age-related macular degeneration; CAP=College of American Pathologists; CLIA=Clinical Laboratory Improvement Amendments.

REVIEW NEWS
Volume XXI • No. 12 • December 2014

Actavis/Allergan Union Ends Months of Takeover Turmoil

Specialty pharmaceutical company Actavis and Allergan last month entered into a definitive agreement under which Actavis will acquire Allergan. The transaction is valued at approximately $66 billion, and will create one of the top 10 global pharmaceutical companies by sales revenue, with combined annual pro forma revenues of more than $23 billion anticipated in 2015. The transaction has been unanimously approved by the Boards of Directors of Actavis and Allergan, and is supported by the management teams of both companies. Allergan had for months been the target of a takeover attempt by Valeant Pharmaceuticals.

"We will establish an unrivaled foundation for long-term growth, anchored by leading, world-class blockbuster franchises and a premier late-stage pipeline that will accelerate our commitment to build an exceptional, sustainable portfolio," said Brent Saunders, CEO and president of Actavis. "The combined company will have a strong balance sheet, growing product portfolios and broad commercial reach extending across 100 international markets. Our combined experienced management team is dedicated to driving strong organic growth while capturing synergies and maintaining a robust investment in strategically focused R&D." Based in Dublin, Ireland, Actavis has U.S. headquarters in Parsippany, N.J.

David Pyott, chairman and CEO of Allergan, added, "Today's transaction provides Allergan stockholders with substantial and immediate value, as well as the opportunity to participate in the significant upside potential of the combined company. We are combining with a partner that is ideally suited to realize the full potential inherent in our franchise. Together with Actavis, we are poised to extend the Allergan growth story as part of a larger organization with a broad and balanced portfolio, a meaningful commitment to research and development, a strong pipeline and an unwavering focus on exceeding the expectations of patients and the medical specialists who treat them. I am thankful for the hard work and dedication of our employees, and I'm confident they will make many valuable contributions to the combined company. Looking to the immediate future, all of us at Allergan are excited to roll up our sleeves and work closely with the Actavis team to ensure a smooth transition."

The combined company will be led by Mr. Saunders. The integration of the two companies will be led by the senior management teams of both companies, with integration planning to begin immediately in order to transition rapidly to a single company. The combined company will provide a strong commitment to R&D, with an annual investment of approximately $1.7 billion, focused on the strategic development of innovative and durable value-enhancing products within brands, generics, biologics and OTC portfolios. The combination is expected to add approximately 15 projects in near- and mid-term development to Actavis' robust development portfolio.

The transaction is subject to the approval of the shareholders of both companies, as well as customary antitrust clearance in the United States, the European Union and certain other jurisdictions, and is anticipated to close in the second quarter of 2015.

AMD Risk Score From OCT Data

Stanford University scientists have found a new way to forecast which patients with age-related macular degeneration are likely to suffer from the most debilitating form of the disease. The new method predicts, on a personalized basis, which patients' AMD would, if untreated, probably make them blind, and roughly when this would occur. Simply by crunching imaging data that is already commonly collected in eye doctors' offices, ophthalmologists could make smarter decisions about when to schedule an individual patient's next office visit in order to optimize the chances of detecting AMD progression before it causes blindness.

Until now, there has been no effective way to tell which individuals with AMD are likely to progress from the dry to the wet stage. Current injection treatments are costly and invasive, precluding the notion of treating people with early or intermediate stages of AMD. Doctors and patients have to hope the next office visit will be early enough to catch wet AMD at its onset, before it takes too great a toll. In a study published in the November

Correction

The November 2014 article "In the Dry-Eye Pipeline: Slow Progress" incorrectly indicated that lifitegrast manufacturer Shire had submitted clinical trial data to the Food and Drug Adminstration, and that the data was under review. In fact, Shire intends to submit a New Drug Application for lifitegrast as a treatment for the signs and symptoms of dry-eye disease in adults in the first quarter of 2015.

Review regrets the error.

issue of *Investigative Ophthalmology & Visual Science*, the researchers derived a formula that they say predicts, with high accuracy, whether a patient with mild or intermediate AMD will progress to the wet stage. The formula distinguishes likely from unlikely progressors by analyzing patient data that's routinely collected by spectral domain optical coherence tomography.

"Right now, a patient who goes into the ophthalmologist's office typically gets an SD-OCT scan anyway," said the study's senior author, Daniel Rubin, MD, assistant professor of radiology and of biomedical informatics. "Our technique involves no new procedures in the doctor's office—patients get the same care they've been getting anyway. We've simply added on a computerized image-processing step that analyzes not only that scan but any previous ones available from that same patient's earlier visits."

From this computerized analysis, the investigators are able to generate a risk score: a number that predicts a patient's likelihood of progressing to the wet stage within one year, three years or five years. The likelihood of progression within one year is most relevant, because it translates into a concrete recommendation: how soon to schedule the patient's next office visit.

Until now, attempts to predict AMD progression have relied on eye doctors examining color photographs of the retina taken in their offices. There is no way to translate that information

into risk scores. The high-resolution imaging technique, Dr. Rubin said, provides much richer detail. "You can almost see individual cells," he said. Plus, it is far more amenable to digital analysis. Previously proposed predictive models have shown some accuracy over long periods of time, but none has been adequately accurate over the shorter, one-year time frame that's relevant to making decisions about office-visit frequency, Dr. Rubin said.

The Stanford team analyzed data from 2,146 scans of 330 eyes in 244 patients seen at Stanford Health Care over a five-year period. They found that certain key features in the images, such as the area and height of drusen, the amount of reflectivity at the macular surface and the degree of change in these features over time, could be weighted to generate a patient's risk score. Patients were followed for as long as four years, and predictions of the model were compared with actual instances of progression to wet AMD. The model accurately predicted every occurrence of progression to the wet stage within a year. About 40 percent of the time when the model did predict progression to wet AMD within a year, the prediction was not borne out.

"No test gets it right 100 percent of the time," Dr. Rubin said. "You can tweak the model to trade off the risk of telling someone they will progress when they actually won't against the risk of telling them they won't progress when they actually will. With AMD you really don't want any false negatives, so you tune the model accordingly. The downside is that some patients will wind up being told to come in sooner than, in fact, they probably need to. But that's nothing compared with the downside of a patient at high risk for progression's not coming in soon enough." Dr. Rubin emphasized that this proof-of-principle study needs to be followed up by a larger study, ideally using data gathered from patients seen at other institutions. He and his associates have begun such a study.

Medicare Billing Status Passed for Omeros' Omidria

Omidria (phenylephrine and ketorolac injection, Omeros) 1%/0.3%, approved earlier this year by the Food and Drug Administration for use during cataract surgery or intraocular lens replacement, has received transitional pass-through status from the Center for Medicare & Medicaid Services.

Transitional pass-through status will allow ambulatory surgery centers and other outpatient facilities to bill Medicare and other insurance providers for

REVIEW of Ophthalmology

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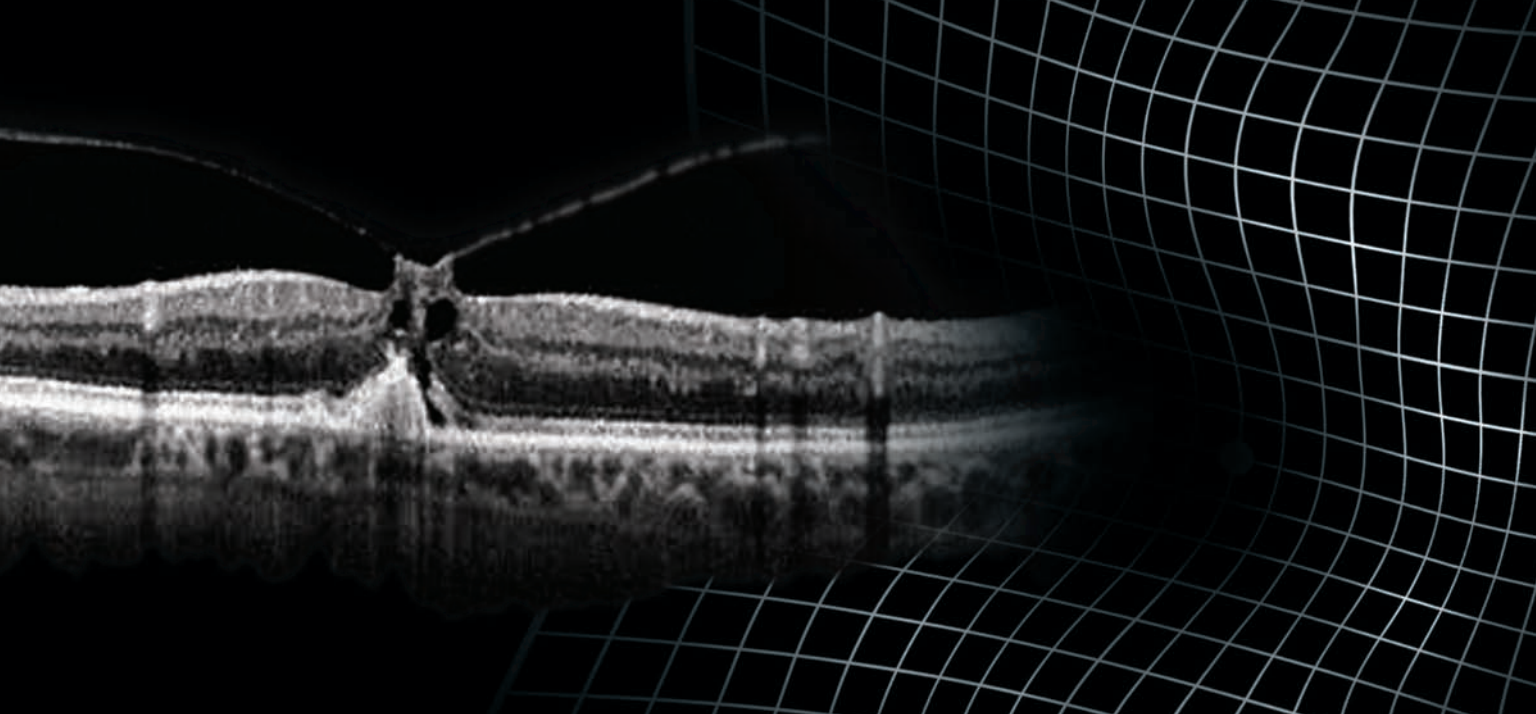

SYMPTOMATIC VITREOMACULAR ADHESION (VMA)

SYMPTOMATIC VMA MAY LEAD TO VISUAL IMPAIRMENT FOR YOUR PATIENTS[1-3]

IDENTIFY | Recognize metamorphopsia as a key sign of symptomatic VMA and utilize OCT scans to confirm vitreomacular traction.

REFER | Because symptomatic VMA is a progressive condition that may lead to a loss of vision, your partnering retina specialist can determine if treatment is necessary.[1-3]

THE STEPS YOU TAKE TODAY MAY MAKE A DIFFERENCE FOR YOUR PATIENTS TOMORROW

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References: 1. Sonmez K, Capone A, Trese M, et al. Vitreomacular traction syndrome: impact of anatomical configuration on anatomical and visual outcomes. *Retina*. 2008;28:1207-1214. **2.** Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. *Am J Ophthalmol*. 1995;119(1):55-56. **3.** Stalmans P, Lescrauwaet B, Blot K. A retrospective cohort study in patients with diseases of the vitreomacular interface (ReCoVit). Poster presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2014 Annual Meeting; May 4-8, 2014; Orlando, Florida.

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Omidria using a temporary Healthcare Common Procedure Coding System code unique to Omidria. Pass-through status allows for separate payment for new drugs and other medical technologies that meet specific clinical-value and cost requirements. Pass-through status for Omidria will become effective on January 1, 2015, and will remain in effect for two or three years, after which CMS and other insurance providers will make a new reimbursement determination. Reimbursement will be based on the product's wholesale acquisition cost of $400 to $500 per single-use vial.

"The recent approval of pass-through reimbursement for Omidria means that surgeons, surgicenters, and patients will have no additional costs associated with the use of Omidria," says Eric Donnenfeld, MD, of Ophthalmic Consultants of Long Island. "There will be direct reimbursement to the surgicenter by Medicare. This is a win/win for surgeons and patients. We will be able to use an FDA-approved product during cataract surgery that improves surgical outcomes and the patient experience with the cost of the medication being paid directly by Medicare."

Omidria is the only FDA-approved product for intraocular administration that prevents intraoperative miosis and reduces postop pain. In a recently published study, it was found to maintain mydriasis, prevent miosis and reduce early postop pain when administered in irrigation solution during intraocular lens replacement, with a safety profile similar to that of placebo.

According to Dr. Donnenfeld, Omidria fills a significant unmet need in ophthalmology. "This is the first FDA-approved product designed to prevent pupillary miosis and reduce postoperative ocular pain to create a more tolerable patient experience," he says. "The combination of intracameral phenylephrine and ketorolac will not only improve surgical results, but will also improve both the patient and surgeon experience in the operating room. Predicting who will develop pupillary constriction is difficult, if not impossible, and once the pupillary constriction begins, the surgeon has to change his technique and sometimes stop in the middle of the procedure. Pupillary constriction may convert a conventional cataract surgery into a complex case that requires urgent and specialized treatment that wasn't previously expected. In addition, successful surgeons pay attention to the patient experience. Omidria is an important step in moving surgeons from conventional to refractive cataract surgery."

The company plans to launch Omidria no later than early 2015. REVIEW

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An interdisciplinary faculty of ophthalmic sub-specialties will review the continuing progress in Cataract and Refractive Surgery, Glaucoma, Retina, Neuro-Ophthalmology, Oculoplastics, Ocular Surface Disease, Cornea and Oncology.

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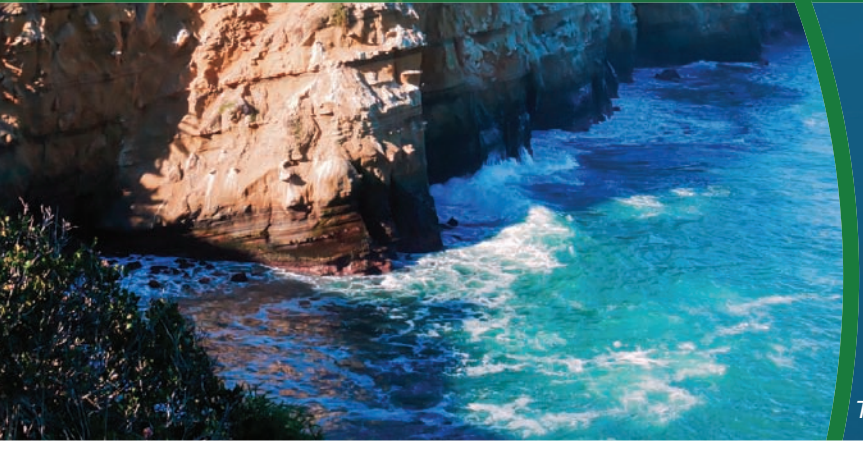

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Departments

Cover Focus

Donna McCune, CCS-P, COE, CPMA

The Benefits of Scribes For Your Practice

With some practice and a few EMR considerations, scribes can help increase both productivity and workflow.

Q What is a scribe and why would a practice utilize one?

A A scribe is a medical assistant who transcribes into the medical record what a physician dictates while an exam takes place. Scribes may not elaborate on or make extraneous notations into the medical record based on their own interpretations. In addition, a scribe assists the physician in locating tests or prior-visit information pertinent to the encounter.

There are many reasons why practices utilize scribes. In addition to efficiencies, scribes allow physicians to focus their attention on the patient while the exam takes place and ensure that documentation in the medical records does not suffer. For paper charts, a scribe may improve legibility. For both paper and electronic records, a scribe may improve the quality and quantity of the notes.

Q Can scribes improve productivity?

A Yes. For a practice that has never utilized scribes, changes to processes and flow need to occur before the practice will see improved productivity. But, with the support of physicians, well-trained scribes integrated into a workflow that utilizes them to their full potential can increase a physician's productivity.

Q Are there restrictions on what a scribe can record in the medical record?

A Organizations such as healthcare systems, teaching facilities and hospitals generally have different requirements regarding the use of scribes. There may be differences between inpatient and outpatient settings. A scribe cannot document some services, such as extended ophthalmoscopy; only the physician can make accurate retinal drawings.

Q Do Medicare Administrative Contractors provide any guidance or policies for the use of scribes?

A Some do, so it is best to check with the relevant MAC. For example, First Coast Service Options, MAC for Florida, provides this answer to the frequently asked question on their website:

"Medicare policy is not opposed to the use of personnel as scribes. However, the medical record must include documentation that the physician reviewed and confirmed the information stated by the scribe."

Novitas, the MAC for several states, says that while the physician must perform the service,

" … the scribe may document what is dictated and performed in the medical record. Documentation of scribed services must clearly indicate:

- who performed the service;
- who recorded the service;
- the qualifications of each person (i.e., professional degree, medical title); and
- be signed and dated by both the physician … and scribe."

Q If the MAC does not provide any specific guidance, is it necessary for the physician to document that a scribe entered the data into the medical record?

This article has no commercial sponsorship.

A Even when there is no specific instruction, the physician should attest to the accuracy of the scribe's note. A physician might write, "I agree with the above documentation" or "I agree the above information is accurate and complete" to show that the notes in the medical record have been reviewed by the physician and are as intended. The absence of an attestation may cast doubt on the accuracy of the record. In electronic medical records, there should be a mechanism for the physician to indicate that the scribe's entries were reviewed and verified.

Q Are there other considerations for scribes when the practice utilizes EMR?

A Yes. While EMR tracks, via log-in, who makes entries in the medical record, it does not make it clear if that person is a scribe, technician or physician. For this reason, best practices include requiring that:

- scribes log in to document information dictated by the physician;
- physicians log in to sign charts (do not allow scribes to sign charts for physicians); and
- physicians review, edit and correct the scribe's notations and attest to the completeness and accuracy of the record.

Additionally, passwords should be kept confidential—do not share passwords between physicians and staff.

Scribing is different from taking measurements such as visual acuity or intraocular pressure; the same person should not perform these functions concurrently. If the person can function as both a scribe and tech, consider two different log-in passwords to facilitate the distinction for reviewers.

Q Do scribes require certification or other special training?

A Not yet. According to Novitas' *Scribe Services Guidelines*, published in their December 2011 Medicare Report, "a scribe can be a Non-Physician Practitioner (NPP), nurse or other ancillary personnel allowed by the physician to document his/her services in the patient's medical record." Novitas requires "…the use of a scribe to be clinically appropriate for each situation and in accordance with applicable state and federal laws governing the relevant professional practice … [and] any other relevant regulations."

Scribes should have legible handwriting, familiarity with data entry and present a professional appearance. Although not responsible for code selection, scribes should have a working familiarity with ICD coding.

Q For the purposes of achieving meaningful use with electronic health records, are there any limitations associated with the use of a scribe?

A Yes. One of the meaningful use core measures is "Use computerized physician order entry (CPOE) for medication orders." The Stage 1 CPOE rules state,

"Any *licensed* [emphasis added] healthcare professionals can enter orders into the medical record … for the objective of CPOE if they can enter the order per state, local and professional guidelines. The order must be entered by someone who could exercise clinical judgment in the case that the entry generates any alerts about possible interactions or other clinical decision support aides. This necessitates that the CPOE occurs when the order first becomes part of the patient's medical record and before any action can be taken on the order. Each provider will have to evaluate on a case-by-case basis whether a given situation is entered according to … [the above]."

The key word is "licensed;" as discussed, scribes are not licensed.

Q Will the rules for Stage 2 meaningful use allow the scribe to use CPOE for medication orders?

A The new final rule for Stage 2, published on September 4, 2012, altered who is authorized to enter CPOE orders:

"Any licensed healthcare professional or credentialed medical assistant, can enter orders into the medical record for purposes of including the order in the numerator for the objective of CPOE if they can originate the order per state, local and professional guidelines. Credentialing for a medical assistant must come from an organization other than the organization employing the medical assistant. The revision allowing MAs to enter CPOE orders is available for reporting years 2013 and beyond regardless of the Stage of Meaningful Use."

Q Are there specific types of certification that qualify the scribe to enter CPOE orders?

A No. The Centers for Medicare & Medicaid Services did not specify a certifying body. CMS' only requirement is that the source of the credential(s) be an organization different from the employer. Examples include a medical assistant degree or certification from an organization such as the American Association of Medical Assistants, the Joint Commission on Allied Health Personnel in Ophthalmology or the American College of Medical Scribe Specialists. This list is not exhaustive of certifying entities. REVIEW

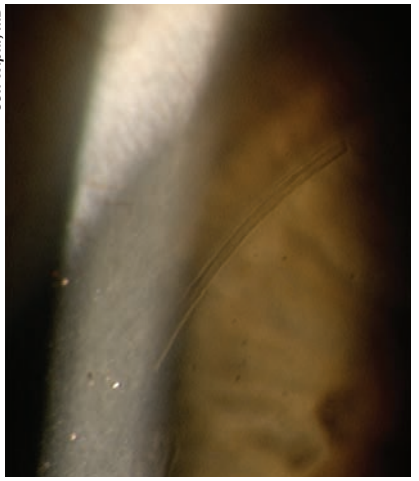
Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.


Honing Intrastromal AK Nomograms

Surgeons say these new incisions can help if toric lenses aren't an option or don't treat all of a patient's astigmatism.

Walter Bethke, Managing Editor

Among the new techniques the femtosecond laser has brought to surgeons is the ability to make incisions within the cornea without the need to break the epithelium or Bowman's, avoiding the risk of wound problems and possible overcorrections. Surgeons discovered, however, that the rules for these intrastromal cuts are a bit different from the ones for incisions that are open, especially in terms of the amount of refractive effect they can achieve. Here, surgeons familiar with these cutting-edge incisions discuss their pros and cons, and what nomograms they're currently using.



Jeff Wipfli, MD

An intrastromal incision has less effect than one on the surface, but surgeons say this helps avoid overcorrections.

AMO Catalys

Users of the Catalys were recently given a new option for planning their intrastromal incisions in the form of a website, femtoemulsification.com, developed by London surgeon Julian Stevens and based on his personal nomogram.

"With these intrastromal incisions—which I like to call cylinders—there's no risk of infection and there's a very fast visual recovery and healing compared to manual incisions," Dr. Stevens says. "Stabilization of the vision is much quicker, and by a month it's actually not bad. There is a little bit of a foreign body sensation, because the cylinders can tickle some of the corneal nerves and even transect some of them. So, you do get an inflammatory response. If you just do these cylinders, then you don't need antibiotic drops but you do need some anti-inflammatories."

One of the general limitations of these intrastromal incisions is that they don't achieve the same magnitude of effect as a similar-sized incision that breaches the surface. "A new nomogram needed to be built," says Dr. Stevens. "For this nomogram, I lifted my original nomogram for intrastromal femtosecond incisions with the IntraLase and fed it into the system, creating version 1 nomogram for the Catalys. I then used my results to build version 2, then the current version 3."

To use the website, you enter in data in the fields provided, such as the amount and axis of the preop astigmatism the location and length of your usual entry wound and how much astigmatism it induces, and the nomogram will generate the length of two symmetric arcs and the meridian on which they should be made. On the laser, the cylindrical incisions are placed in a space between 20 and 80 percent of the corneal depth, at an 8-mm zone, based on optical coherence tomography of the Catalys. You also have to adjust the laser's setting beforehand for optimal results. "You deliberately increase the power of

This article has no commercial sponsorship.

the laser during the intrastromal application," explains Dr. Stevens. "That creates extra gas in the cornea that separates the cylinder's edges. This is quite important because if there are any extra bridges of tissue the cylinder won't open fully and achieve its effect. Some patients' eyes are quite kinetic and of course there are always micro-movements that can result in some tissue bridges." Dr. Stevens says the current intrastromal nomogram generates a mean vector magnitude of correction of 83 percent of the intended amount, up to a maximum of 2.5 D. He says the incisions achieve greater effect in the elderly and less in younger patients. In fact, the website will display a warning when the data is entered for a younger patient, informing the surgeon that the procedure may not achieve the entire amount of correction.

Since the initial version of the software is based on his work with the IntraLase, Dr. Stevens says the nomogram can also be transferred to that device. "With the IntraLase, you use an OCT ahead of time and then program the laser from a percentage depth approach," he says. "The difference is you have to manually enter the planning into the IntraLase screens. It's quite a bit of typing. Also, it's important to scrutinize the screen marked 'Review' on the IntraLase to make sure you didn't put in any incorrect values."

Alcon LenSx

Users of the LenSx are also creating intrastromal astigmatic incisions, and are refining their nomograms.

Jeffrey Wipfli, MD, of St. Luke's Eye Center in Tampa, Fla., has hit upon an approach that's been working well for him. "We use the AMO LRI calculator and I've been using the Nichamin nomogram," he explains. "I used to initially open all of my LRIs right off the bat in the OR. I didn't find that it made a huge difference so I stopped doing that. So, in some ways, you could call it intrastromal in that we're not breaking through the epithelium. I aim for 80 percent of what the nomogram recommends based on the work of Eric Donnenfeld and the fact that the incisions are more central than the LRIs we would do before. I use a 9-mm optical zone. The length and depth are a lot more accurate, so to prevent overcorrections we were shooting for about 80 percent of what was predicted by the nomogram. I've adjusted the nomogram slightly, based on the posterior corneal astigmatism issue that has come up with toric lens implants, because I found I was not quite getting as much treatment effect as I would have liked. What I'm doing now is shooting for about 90 percent when the astigmatism is against-the-rule, but I'm still doing 80 percent in patients who have oblique or with-the-rule astigmatism." He says he programs the laser's OCT to start creating the incisions at 90 percent of the corneal depth.

Dr. Wipfli says one of the benefits of the intrastromal incision approach is that if there's an undercorrection postoperatively, he's still got a few options. "I wait a week postop to see what the effect is," he says. "If it appears that the patient is undercorrected, then I'll take a small Slade spatula and open the incisions at the slit lamp. This can get between a 0.25- and 0.5-D boost. It's rare that I need to do that, however."

Dr. Wipfli says a challenge with intrastromal incisions in general is avoiding intersecting the cataract entry wound or the paracentesis. "I try to create paired incisions, if possible, without having to adjust my main incision or my paracentesis," he says. "If it looks like I will bisect one of my other incisions, I'll do a single LRI, up to a 45 degree arc length. I did a longer incision once, 60 degrees, that caused some irregular astigmatism and overcorrection, so 45 degrees is as long as I will go. If the patient needs any more correction later, I can either open it at the slit lamp or add a second one manually and pair it with the other."

In terms of the maximum amount of correction, Dr. Wipfli says he thinks surgeons could get up to 2 D with paired limbal relaxing incisions, but that he typically doesn't do that. "For between 1 and 1.5 D of preop astigmatism, I'll usually choose between a toric lens or a LenSx LRI depending on the axis of the astigmatism," he says. "However, I feel comfortable with up to about 1 D with against-the-rule and a little bit more—1.25 D—with with-the-rule with the LenSx. So over 1.5 D I'll usually use a toric lens. I think that is more accurate and reproducible."

B + L Victus

London surgeon Sheraz Daya says the Victus femtosecond laser can also create intrastromal cuts, as long as you know how to set it up.

"The way the Victus cuts, it starts posteriorly and moves anteriorly," explains Dr. Daya. "So, you need to instruct it where to stop. Usually, for an incision that penetrates the surface, you want to go through-and-through and up into the patient interface, which is set as the 'zero' point in the system. That way you know you're through Bowman's layer. To do this, you program an offset of, say, +50 µm, which ends the cut at 50 µm into the interface. To perform an intrastromal incision, instead of setting a +50 offset you program a -50-µm offset, which means the incision stops below the interface."

Overall, Dr. Daya says that, though there are some purported advantages to intrastromal astigmatism treatment, he currently leans more toward creating more conventional incisions that break the surface. "With intrastromal, you're not breaking through Bowman's, you have no incisions that

can cause patients discomfort and, theoretically, there is no risk for corneal infiltrates or epithelial breakdown," he says. "I haven't seen any infiltrates or breakdown with other femtosecond incisions that open on the surface, though. I have had some open astigmatic keratotomy incisions that went on to be overcorrected and which I've had to suture, which is a situation you'd avoid with intrastromal cuts.

"However, I've done intrastromal incisions at a 7-mm optical zone in corneal graft patients," Dr. Daya continues. "And I've experienced a lot of instability with them. Initially they wouldn't get any effect, and then the patient would come back six months later not being able to see well. It would turn out they had 4 D of correction. For me, I find non-intrastromal LRIs more stable."

Nichamin LRI Nomogram, Modified for Intrastromal

Astigmatism (D)	Paired incisions (degrees) at 9-mm zone and 90-percent depth for patient age groups		
	51 to 60 years old	61 to 70 years old	71 to 80 years old
0.75	WTR: 27 ATR: 28	WTR: 25 ATR: 26	WTR: 23 ATR: 25
1	WTR: 33 ATR: 36	WTR: 31 ATR: 33	WTR: 28 ATR: 31
1.25	WTR: 38 ATR: 41	WTR: 36 ATR: 37	WTR: 33 ATR: 35
1.5	WTR: 43 ATR: 46	WTR: 40 ATR: 42	WTR: 37 ATR: 39
1.75	WTR: 48 ATR: 51	WTR: 44 ATR: 47	WTR: 41 ATR: 43

WTR: With-the-rule
ATR: Against-the-rule

Manila, Philippines, surgeon Harvey Uy uses a slightly tweaked version of the Nichamin nomogram when treating astigmatism with his LensAR femtosecond laser. He uses a 90-percent depth rather than 85 percent.

LensAR

Manila, Philippines, surgeon Harvey Uy says the femtosecond LRI nomograms for non-intrastromal incisions developed by Louis Nichamin, MD, have served LensAR users well thus far when they attempt intrastromal cuts.

Even though conventional wisdom holds that you get less of an effect with an intrastromal cut if you use a nomogram meant for a normal, surface incision, Dr. Uy says it actually fits his approach to treating astigmatism. "I follow the same nomogram because, in general, I'd rather be undercorrected than overcorrected," he says. "The nomogram is based on 90-percent depth and a 9-mm optical zone. The LensAR system will measure the corneal thickness and then the software will automatically set it to begin the incision at 90-percent depth. You can change the setting to other depths, as well as alter the optical zone, however. We like the 9-mm zone because it's farther from the visual axis."

Though the depth, optical zone and cutting are automated, Dr. Uy says the surgeon has to use his manual skills to get the axis correct. "Now, we basically put a reference mark on the eye," he says. "You also have a reference mark on the patient interface. You align the two marks, then do the imaging and pre-program the incision locations. Though it works, it is subject to some errors when marking the reference points. You'll probably be off by a few degrees, which can lead to suboptimal astigmatic correction in some cases. However, LensAR is currently developing new iris registration software so that a diagnostic machine will capture an image of the patient's eye preoperatively. The image of the eye will be sent to the femtosecond laser to let it determine the correct treatment axis."

In terms of correction, Dr. Uy says he can treat up to 3 D of preoperative cylinder with these intrastromal incisions. "However, if someone has over 1.5 D, we encourage him to get a toric intraocular lens," he says. "Even so, there will be some patients who get the toric lens but whose astigmatism still exceeds the power of the IOL. In those cases, we'll use the arcuate incision to supplement the toric IOL and correct larger amounts of astigmatism."

Dr. Uy says one aspect of intrastromal femtosecond incisions he likes is the titratability in cases of undercorrection. "The disadvantage of an incision that opens is you may overcorrect the astigmatism and you can't really undo it," he says. "Whereas if you do intrastromal and you're undercorrected, you can still open it up after the surgery and titrate the correction. The percentage of patients in my practice who need to have the incisions opened later on is about 10 to 15 percent. I've found that patients are generally happy after the procedure. It's the patients who get multifocal lenses who are a bit more particular about correcting their astigmatism."

Dr. Uy says that, though intrastromal ablations take a bit more customization to perform, they have their uses. "I think it's a very safe procedure," he says. "We haven't had any complications from it, and haven't seen any perforations. If a surgeon has a femtosecond laser, I'd encourage him or her to use this particular feature." REVIEW

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

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

Indications and Usage

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

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

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

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

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

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

Preservative-Free

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

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

Istalol®
(timolol maleate ophthalmic solution) 0.5%

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

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

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

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

6.2 Postmarketing Experience

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION

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

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The Secret to a Satisfied Patient

Walter Bethke, Managing Editor

With technical skill seen as a given, communication skills come to the forefront.

Jean-Paul Sartre once wrote, "Hell is other people," and the patients who fill out satisfaction surveys would agree. Despite medicine's cutting-edge technology and excellent technical outcomes, time and again it's the personal interaction with doctors and staff—the other people—that patients define as the deciding factor influencing their satisfaction with their care. When a staff member is brusque, things aren't explained properly or wait times seem long, patients take note. To find out what surveys have identified as key factors influencing satisfaction, and how some practices may be able to improve satisfaction, read on.

> **"Feeling listened-to correlates highly with a willingness to recommend a practice."**
>
> —Meryl Luallin

Communication Arts

Meryl Luallin, a partner at the SullivanLuallin Group, a firm that helps practices improve the patient experience, says that analyzing the 20 years of surveying has taught her some lessons. "We're the preferred vendor for patient satisfaction surveys for the Medical Group Management Association, so we have a large database of patient responses," she says. "After doing a regression analysis of our survey data, we identified the key drivers for both overall satisfaction with a practice as well as the likelihood of recommending a doctor to others. The number-one factor was the provider listening to the patient. Patients feeling listened-to correlates especially highly with a willingness to recommend a practice. The second-highest factor is 'The doctor had respect for what the patient had to say.' " Mrs. Luallin has distilled her learnings about ways to improve the patient experience into the acronym CLEAR, or Connect, Listen, Explain, Ask and Reconnect. *(Specific actions that fall under the CLEAR subject areas appear in Table 1, pp. 22.)*

Jeff Machat, MD, an anterior segment surgeon in Toronto, says listening to patients is key during an initial consultation about LASIK. "People who are nearsighted will tell you that they don't have a problem with read-

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ing, just with distance, so 'just fix that and don't touch my reading ability,' " he says. "Meanwhile, we all know that when you get rid of nearsightedness, they'll then be presbyopic and miserable. It's important to understand how a patient imagines his life after surgery, and what the procedure's limitations are, so the result you give him will work for him. We need to have long conversations with people so they really understand what we're talking about, too."

The third highest influential factor in Mrs. Luallin's database was the helpfulness of the practice's staff, such as the physician's assistants and receptionists. Paul Lee, MD, chair of ophthalmology at the University of Michigan, says patient satisfaction or dissatisfaction often begins with these individuals. "A big driver of satisfaction is the communication skill of the entire team," he says. "It's not just the physician. In most practices, there is an integrated team that starts with the person who greets the patient when he comes in; it could be a clerk or someone in a central lobby who helps people find their way. We view this as a team priority, that everyone who has an interaction with the patient and/or his family plays a part in helping create satisfied patients."

As part of her job, Mrs. Luallin will shadow doctors at their clinics, or sometimes play the role of a mystery patient, in order to advise them on ways they can improve patient satisfaction. One shadowing session stands out in her memory. "At the beginning of an exam, the middle-aged, female patient told the doctor she had a painful lump in her breast," Mrs. Luallin recalls. " 'When did the pain start?' the doctor asked. 'It was in March,' the patient responded. 'My mother had died, and then in November my sister died, and my best friend passed away, too. Last year was a horrible year for me.' 'Wow,' the doctor replied. 'So, when did the pain start?' This is not uncommon; doctors will tune out all other aspects of the patient interview and just focus on what they need for the diagnosis. It's the practices who have trained their staff to be caring and come across as personally interested in the patients that score the high ratings."

Toronto's Jeff Machat, MD, says good interpersonal communication is key.

For physicians interested in another reason to dislike electronic health records, they need look no further than the cooling effect they have on doctor-patient interaction. It's hard to be warm and engaging while you're looking away from the patient and typing data into a computer. Experts say there are some ways to counteract this negative effect, though. "Look at the patient when you speak or ask a question," says Mrs. Luallin. "Then, as you type, reassure the patient by saying, 'I'm entering your information into the record, but I'm listening.' "

Dr. Machat is aware of the effect of EHR on patient interaction, and takes steps to help mitigate it. "I have both EHR and paper," he says. "I actually have a scribe in the room, which lets the patient know someone is taking notes and also allows me to focus on him. I always try to put myself at eye level with patients and look them in the eye so they know they have my full attention. Then, once they leave, that's when I write my notes. So, EHR is amazing and wonderful, but not at the expense of looking someone in the eye and making him feel important."

Dr. Lee conducted a study of patient-centered care in ophthalmology, with a particular emphasis on patient expectations.[1] Part of the paper involved patient focus groups that allowed individuals to identify the most important things they expected and appreciated when they visited the ophthalmologist. "The top desire was for honesty," Dr. Lee avers. "The second was information about their individual diagnosis and prognosis. Third was receiving an explanation in a clear language. The fourth-ranked expectation involved an issue of skill: The doctor's reputation and experience. However, the fifth- and sixth-ranked expectations go back to communication and relationships, specifically empathy and how well the practice listened to, and addressed, their concerns. So, five of the top six key expectations involved how well the physician and his staff relate to patients, rather than his or her skills."

Mrs. Luallin says her firm's surveys have found an interesting effect of expectations on satisfaction. "An analysis of our database has found that first-time patients rate a physician experience lower than existing patients do," she says. "We assume this is because existing patients have learned what to expect and have lowered their expectations. As an aside, when we speak to practices and patients about what causes many complaints, the answer is often unmet expectations. We all experience this even outside of medicine, such as when we travel and have bad experiences with a hotel's service that didn't meet expectations. The bottom line is, if patients have an expectation and it's unmet, such as the expectation that the doctor would take some time with them but instead rushed in and out in five minutes, they could be a little bit disappointed, and this will show up in the ratings."

Dr. Machat takes issues of trust

and honesty, which ranked high in Dr. Lee's study, to heart when consulting with a prospective LASIK patient. "We don't tell patients that anything is guaranteed and that they shouldn't worry," he says. "I look them in the eye and tell them that 99 percent of the time, everything goes great, 1 percent of the time we have a problem and one in 1,000 times we have a serious problem. These problems will affect the sharpness, crispness and clarity of their vision permanently. When patients come to you for a surgery like LASIK, they already know there are risks. If you tell them there are no risks, that reduces your credibility, and they want to trust you."

Surgical Satisfaction

Experts say the need for good communication doesn't stop at the exam lane, but instead continues right to the operating room.

When Dr. Machat was with TLC Laser Eye Centers he says they conducted many surveys and, once again, communication was a key finding. "The number-one factor was the patient not getting the visual result he was looking for," Dr. Machat says. "He may have gotten 20/30 or 20/25 and felt he paid a lot of money and really wanted 20/20. The number-two factor was having to wait too long. Third was when he felt like just a number, like someone on a conveyor belt. And then in spots four through 10, it was all about human interaction. Oftentimes, these complaints would be that they didn't feel the surgeon gave them enough time, understood them or listened to them. They'd also complain that the surgeon didn't talk them through the surgery. So, overall, nine out of 10 issues had to do with interpersonal interactions. This led me to understand that, as a staff member, if you're having a bad day you still have to muster up a smile. That's how a patient wants you to feel about their care."

Table 1. A CLEAR Path to Patient Interaction

CONNECT	Acknowledge patients immediately, even non-verbally if need be.
	Use eye contact and smile.
	Introduce yourself, and tell them what your job is (if appropriate).
	Wear your name badge so patients can read it.
	Use the patient's name.
	Keep your voice warm and welcoming. Be polite. Say, "please," and "thank you."
LISTEN	Maintain eye contact and a pleasant expression.
	Use head nods to indicate that you're paying attention.
EXPLAIN	Tell patients what you're doing.
	Use simple language (not abbreviations or acronyms).
	Tell patients what's going to happen.
ASK	Ensure the patient's comfort with information, surroundings.
	Ask if the patient has other questions.
RE-CONNECT	Check with roomed patient every 10 minutes and say, "Thanks for your patience."
	Acknowledge patients/others as they depart saying, "Take care."

"There's a phrase that's popular in patient satisfaction: Narrate the care," says Mrs. Luallin. "This involves telling the patient what you're going to do or are doing as you do it." Dr. Machat thinks this is key to managing a patient's trepidation during surgery. "When the surgical patient arrives at prep, I have an amazing staff who will calm him down dramatically," he says. "They distract him with conversations about his life, and inform him about what to expect during the procedure, going through the steps, and telling him the dos and don'ts. By the time the patient sees me, he's in great shape. Then, during the procedure, I say the word 'perfect' 1,000 times as I describe what I'm doing. 'You're going to feel some pressure now … perfect.' Then, 'Everything's going to be dark … perfect.' I say it so often that when patients sit up and I ask how it was, they'll say 'perfect.' I also have someone count down during every step so the patient knows how many seconds it will take before that step is complete."

As an example of how effective narrating care can be, Dr. Machat recalls one patient who traveled from New York to Windsor, Ontario, in 1993 to have PRK. "She had a low prescription," he recalls, "and we performed PRK. I told her during the case that if everything goes right, her vision will be blurry immediately afterward. When the surgery was done, she sat up and started to cry. I asked if everything was OK and she blurted out, 'I'm so happy—everything is blurry!' So, it's all how you speak to patients."

Ultimately, Dr. Machat thinks one of the keys to satisfied patients is to remember that this is all new to them. "I tell doctors and staff that they have to put themselves in the patient's shoes," he says. "You may have done thousands of cases, but this is the patient's one and only time he's experiencing this. I want patients to feel comfortable, that they can ask us anything, and to know that we're empathetic to what they're going through." REVIEW

1. Dawn A, Lee P. Patient expectations for medical and surgical care: A review of the literature and applications to ophthalmology. Surv Ophthalmol 2004;49:5:513-24.

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INDICATIONS AND USAGE

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Managing Today's Difficult Patients

Christopher Kent, Senior Editor

The advent of personal information technology has madepract icing more challenging than ever. Here's help.

As the world changes ever more rapidly and our information access becomes faster and more all-encompassing, we are all being changed as well. One of the side effects of that evolution has been a shift in the nature of the doctor-patient interaction. Today's patients have access to an astounding wealth of information. In some respects this makes a doctor's job easier—but in other respects it makes the job far more stressful and challenging, as many patients become more difficult to work with.

"Throughout the whole course of medical history there have been difficult patients," says John Pinto, president of J. Pinto & Associates Inc., a well-known ophthalmic practice management consulting firm. "Today, however, they're more educated and much better-informed because of the Internet. Back in the 1970s, only one American out of 10 had a college degree. Now about one-third of all Americans are college-educated; and that, combined with having an encyclopedia in your pocket, means that if you are a difficult patient or someone who is going to dispute the doctor or ask a million follow-up questions, you are well-prepared to do so.

"The number of 'difficult' patients you have will depend on where and how you practice," he continues. "Classically, if you have a LASIK practice, a plastics practice offering elective procedures or a practice located in urban centers, you're going to have more patients who are better educated and more argumentative, bringing new facts to the table and having questions for you."

Mr. Pinto points out that part of the reason for an increase in "difficult" patients is the changing nature of ophthalmology. "It's certainly true that patients are asking more questions than they did before, but you also have to realize that ophthalmology has moved into more elective or quasi-elective spheres such as refractive surgery, advanced IOLs and even optical dispensing," he says. "In these areas the patient knows whether his eyes seem right or not. He knows whether he can see better than he did before. This is not like general medicine or surgery where the treatment provided by the doctor might not be discernable by the patient as having fixed a problem. After many of today's ophthalmological procedures, the patient can decide for himself whether the doctor fixed him or not.

"That's what makes ophthalmology both a blessing and a curse," he says. "It's a wonderful profession because almost every patient is helped by what you do, and the patient knows

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1. Conrad-Hengerer et al. *J Cat Refract Surg.* 2012; Conrad-Hengerer et al, JCRS 2012; 38(11): 1888-94.
2. Fabian E et al. New Phaco Fluidics Control: Case to Prevent Surge. Presented at ESCRS, Sept 2006, London, U.K.

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it. He or she will say, "Hey doc, I'm seeing better, good job!' That's why most ophthalmologists are gratified in their careers; 95 percent or more of their patients are very satisfied with their surgical outcomes, for example. However, that's also what makes it so stinging when a patient comes in on her third postop visit and says, 'I'm not sure this surgery worked for me.' Your first response as a provider of care may be to have your feelings hurt.

"Of course, this applies to every service provider, whether you're a waitress or chef or barber," he notes. "But the potential difficulty of being in this position makes it important to be a witnessing presence, to stand apart from yourself and watch how you're responding to those patients. If your response is a source of discomfort and loss of career satisfaction, then you owe it to yourself and your practice to do something to help you deal with these situations differently."

Patient Survey: Usefulness of Medical Information Sources

Mean scores, scale from 1 ("not at all useful") to 7 ("extremely useful"). (n=512)

Source of medical information	Patients getting health information from the Internet	Patients not getting health information from the Internet
Physician or nurse	6.09	6.19
Internet	5.05	2.29*
Educational program or newsletter sponsored by hospital or HMO	4.5	4.54
Television news	4.22	4.98*
Medical journals	4.03	3.11*
Family	3.95	4.8*
Health or fitness magazine	3.84	3.67
Newspaper	3.83	4.29**
Friends	3.79	4.38*
News magazine	3.67	3.49
Radio	3.42	3.87**

* p<.001 for difference between groups by *t* test
** p<.05 for difference between groups by *t* test

Results of this survey suggest that patients getting information from the Internet appreciate the value of medical journals more—and the value of health information gleaned from family, friends and newspapers less—than patients who don't rely on the Internet for information. (Both groups gave medical professionals the highest scores.) (Based on Diaz, Griffith et al, 2002.)

Information From the Web

There's no question that much of what makes difficult patients seem more difficult today is their unfettered access to the Internet. James J. Salz, MD, clinical professor of ophthalmology at the University of Southern California, Keck Medical School, and in private practice in West Los Angeles, notes that it's not just young people who are using the Internet to research their condition. "Today our Medicare patients in their 70s and 80s have smartphones or iPads and use them to do Google searches," he says. "So individuals who might have been intimidated by a desktop or laptop computer can get exactly the same information from a less-imposing device, which they might also be using to read a book."

Obviously, the most common source of trouble is a patient coming in with incorrect information. Stephen Pascucci, MD, FACS, founder of Eye Consultants of Bonita Springs, in Florida, says this happens fairly often, and he believes the best way to deal with it is to be very confident, knowledgeable and well-informed about what you think is best. "For example, one new patient of mine was aware that she had astigmatism and came in believing she needed a toric lens," he says. "She did need cataract surgery, but she didn't have much astigmatism, and it was a type that might help her with reading after surgery. I showed her the topography and explained why her existing astigmatism wasn't necessarily a bad thing and why I thought a toric lens wouldn't work to her advantage. She understood there was a rationale for my disagreeing with her."

He also notes that one of the best ways to manage patients coming in with incorrect information is to educate your staff so that patients' questions can be answered and misconceptions corrected. "Your staff needs to feel very comfortable answering questions," he says. "This enhances the patient experience and saves the doctor a lot of time, because most of the issues are sorted out before the doctor sees the patient. This also makes sense because in my experience patients are much more comfortable with the staff than with the doctor. They're more apt to ask my staff their questions, and they seem to believe what my staff tells them, as if it's gospel. In our practice that may be partly because we focus on letting the staff develop a relationship with each patient."

Dr. Salz agrees that patients sometimes glean incorrect information from the Internet. "That's OK," he says. "If they're misinformed it only takes a few minutes to straighten them out. A patient may come in very worried because he has a black spot in his field of vision. After surfing the Web he concluded that he has macular degeneration or a detached retina, when it's really just a floater. Patients are often misinformed about cataracts too; they sometimes come in thinking they need surgery right away, when their

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vision is still quite good and they won't need surgery for a while. I see this as a great opportunity for us to teach them and relieve their fear. So I'm in favor of patients searching for information on the Web.

"I'm sure it's possible to get the wrong diagnosis or treatment ideas searching the Internet," he adds, "but I haven't had any patient come in having instituted some kind of treatment that was incorrect based on information they found on the Internet. In fact, they often find the right information. We have patients who have correctly diagnosed that they have a chalazion. They look it up, see what it is and find out that one of the best treatments is putting hot compresses on the eye. So they're already doing the right thing when they see us."

Vance Thompson, MD

Patients today are often impressed only by a great experience in your office; good visual outcomes are simply expected. This office was designed and built with that in mind.

Vance Thompson, MD, assistant professor of ophthalmology at the University of South Dakota School of Medicine and founder of Vance Thompson Vision in Sioux Falls, S.D., believes that, in general, patients getting information from the Internet is a good thing. "The most common cause of a patient being unhappy is unrealistic expectations, and for that reason I don't think it's possible to have too much education," he says. "Patients may come in asking about the negatives, but I don't think anyone has ever asked me about something that didn't actually happen at some point. So they're reading about real concerns; they just have a hard time putting them into perspective, and as a result they may be much too worried about them. If we put those concerns in the proper context, and document the fact that they read about it and that we had a discussion about it, I think it helps our patient education—and also helps us medico-legally."

Dr. Thompson acknowledges that some patients can't be dissuaded from their fears. "If a patient reads frightening things on the Internet, those fears can win out, even if he meets with a balanced doctor who provides balanced information about his concerns," he says. "But if a patient like that doesn't proceed with the surgery, that's probably for the best. In that situation the patient isn't willing to believe the doctor, so that might be a patient you wouldn't want to operate on in any case.

"The reality is, patients are getting information from the Internet, and we really don't have a choice but to embrace it," he concludes. "Are there sources of information that are too positive or negative? Sure. But it's the same thing with word of mouth; a patient might run into an acquaintance or a doctor who is too positive or negative about a procedure and take the comments out of context. So being somewhat misinformed is not really a new phenomenon. It's just that information in general is now much more accessible. In any case, it's requiring us to embrace patient education at an even deeper level, and in general, I think that's a good thing."

Impatient Patients

One reflection of today's "instant gratification" culture is patients being quicker to anger if they have to wait more than a few minutes to see the doctor. "That's especially stressful for the staff," notes Dr. Pascucci. "They get the brunt of patient complaints about this. It also drives the staff a little crazy that patients tend to be nicer when in the presence of the doctor. A few patients do argue with me, but many of them just go after the staff. They think the doctor is the one who has to take care of them, so they don't want to make him or her upset."

Dr. Pascucci says that when a patient does get upset because of an unusual delay, he and his staff go out of their way to apologize and try to neutralize any negativity. "Recently, a patient with a 2:00 p.m. appointment was told by the surgery center that the appointment was at 1:15, so she showed up early and had to wait a long time to

see me," he says. "The technician told me what had happened, so I walked in and apologized for the confusion. I was doing her second eye the following week, so I told her we'd make that appointment right now for whatever time she wanted, and I'd make sure she saw me at that time. That immediately neutralized her anger. The point is that you have to be prepared to deal with anger diplomatically and not just blow it off. Your patients want you to treat them like they matter."

Dr. Thompson believes that the problem isn't so much that today's patients are more impatient. "The reality is that we've drifted from a service economy to an experience economy," he says. "What that means is that good results are not considered exceptional. Today, what really moves people to tell their friends about your practice is the quality of their experience being your patient. That means having a great experience on your website, when talking to your staff on the phone, when they're inside your practice for an appointment and after surgery or treatment. It's only in the past 10 or 15 years that this has really become as important as it is now. Obviously we all want to provide great care. But today, the experience you provide is what really speaks to a patient's heart and soul."

Dr. Thompson has invested a lot in that philosophy. "We built a brand new 34,000 sq. foot facility about 18 months ago," he says. *(See picture, facing page.)* "I also had my CEO trained by Jim Gilmore, one of the authors of the book *The Experience Economy*. I want the patient experience to permeate every step of a patient's journey through our practice."

Simple Waiting Room Strategies

Of course, not every practice can go to such lengths to improve the patient experience. Mr. Pinto offers a number of simpler strategies for minimizing confrontations with difficult patients when waiting times get longer than usual. "The classic service-enhancement tools come to mind," he says. "For example, manage patients' expectations when they check in. Tell patients if you're running behind—or that everything is on time, if that's the case. The front desk person might say, 'We normally like to get our patients in and out of here within an hour or less, but we're running a little bit behind today, so your total time in the clinic is probably going to be more like an hour and 20 minutes. Is that going to work out OK for you?' Saying this helps to minimize the number of disgruntled patients you have to deal with.

"Second, to the extent possible given the current economics of your practice, make the waiting period a pleasant experience for the patient," he continues. "Set up your physical plant to be soothing and calming for your patients. Have an alcove here and there where patients can quietly read if they want to or watch TV if that's their preference. (Admittedly, it will be easier for large practices to do this.) People want comfortable, diverse waiting areas that don't force them to touch other patients and allow them a bit of respite. Pleasant lighting is very important. I've even worked with practices that have used aromatherapy experts to make sure that there's a spa-like ambience. At the least, the front desk staff should keep the reception area clean and tidy."

Mr. Pinto notes that it's important to have refreshments available for patients in case you do run behind. "It doesn't cost much at all to have small bottles of water in a glass-fronted refrigerator in the waiting room," he says. "It doesn't cost much to put out some granola bars in mid-morning when stomachs are starting to grumble. Just having a bowl of apples or a few snacks on a table with a coffee urn makes patients feel more at home, even if they don't avail themselves of

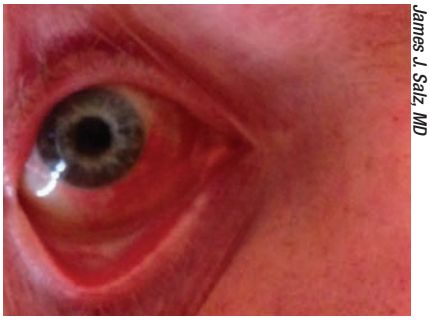
that courtesy. It's a nice gesture. If you see a bunch of apples at the front desk of a hotel, they didn't put them there to feed you. They put them there as a welcoming gesture, to give you a sense that they care about your well-being. Also, if a patient is waiting an unusually long time, a staff member should walk over and ask if the patient needs anything or would like a refreshment."

Mr. Pinto points out that it's important to know what patients will normally tolerate. "Many studies have shown, for example, that patients will usually be fairly patient until about 19 minutes of waiting time has passed. When 20 minutes hits, an alarm goes off in the typical patient's mind, and they start to be unhappy. So it's not a bad idea to make it your goal to manage the throughput of patients so you can keep the primary wait at or under 19 minutes. If you realize you can't manage that, for whatever reason, be sure to let patients know as soon as they come in.

"Ultimately, you need to be aware of what the normal limits are for transit time and waiting time in your type of practice, and do everything possible to stay within those norms," he adds. "That means making sure you're not trying to jam too many patients through a fixed-capacity clinic. I see many practices where, in an effort to keep up economically, the doctors have taken a clinic/staff cohort and infrastructure that's suitable for 50 patients a day and tried to jam 70 patients through every day. Obviously things will bog down if you do that, and it's tougher on the staff, the doctor and the patients. So it's important to be intentional about where you're trying to go with a practice, and not create problems for yourself."

Minimizing Misinformation

One of the best ways to avoid patient problems resulting from misinformation gleaned from the Web is to be proactive about reaching patients with accurate information. These strategies will help:



James J. Salz, MD

Today's technology can be used to your advantage. For example, you can encourage patients calling with visible eye problems to take a smartphone picture and email it to you; it may be clear that the problem is simply a subconjunctival hemorrhage. This patient's condition (above) could have been episcleritis or a subconjunctival hemorrhage, so the doctor had the patient come in for an exam.

• ***Send preop materials designed to offset potential misinformation.*** "I try to create really good preop education materials," says Dr. Thompson. "The current environment requires us to really bring our A game with what we produce so that it's balanced and easy to read, well-organized and not overwhelming. That way patients get to hear our side of the story too."

• ***Direct your patients to websites that will provide accurate information.*** Dr. Thompson points out that if patients are going to search the Web anyway, you can forestall a lot of trouble by pointing them in the right direction. "I always talk with my patients about good websites to visit," he says. "I'm a big fan of allaboutvision.com and the Academy's [American Academy of Ophthalmology's] patient education website, geteyesmart.org."

• ***Aim your social media exposure at all of your patients.*** "Even our senior patients are using social media these days," notes Dr. Thompson. "We're amazed how many seniors are doing email and social media and are on Facebook. Five years ago I don't think that was true, but we've definitely seen a shift."

• ***Make sure your practice's website is information-rich.*** "This is not only a good way to offset less-accurate information found on the Web, it's also an opportunity to convey your practice philosophy," says Dr. Thompson. "That can do a lot to inspire patients to come to see you and stay with your practice."

Dr. Salz uses his website to help relieve the fears of potential LASIK patients who are unsure about the safety of the procedure. "I take advantage of my patients' Internet use by asking them to view an eight-minute video on our website. The video, created by Patient Information Concepts, is called "LASIK on the Front Lines." It tells the story of how Steve Schallhorn got the military to approve the use of LASIK and PRK, which was a major accomplishment. Dr. Schallhorn was a 'Top Gun' pilot before he went into medicine and ophthalmology. We helped train him here at the University of Southern California, and as a fellow his commitment was to change the military's policy on LASIK and PRK. It took him 10 years, but he did it.

"It's an amazing story, because the FDA studies that we did to get PRK and LASIK approved didn't require demonstrating the level of postoperative vision the military wanted," he says. "The military had to be convinced that if your eye had LASIK, it would perform in every way as well as a patient who was born with 20/20 vision. As I tell my patients, it's one thing for you to see well enough to drive down the 405 freeway in L.A.; it's another thing to see well enough to land a Navy jet on an aircraft carrier at night out in the ocean when the carrier is moving. That's a whole different level of vision. Seeing this story on my website really helps when patients are a little apprehensive about LASIK. Once they see that it's widely done for pilots in the Navy and Air

Force and now approved by NASA for astronauts, they're a lot less worried."

• ***Let patients know that if they're concerned about anything they find on the Internet, you're available to talk.*** This will help prevent patients from simply sitting and fretting over negative information they encounter on the Web, notes Dr. Thompson.

• ***If patients haven't seen the information you'd like them to see before they come in, be prepared to provide it while they're waiting.*** "We have iPads in our waiting rooms," says Dr. Thompson. "If a patient hasn't seen our materials, we ask the patient to look at them while waiting. This can save a lot of time correcting misinformation and explaining options during the exam, and facilitates the conversation by getting them as close as possible to my level of knowledge so they can make a balanced decision."

Get Your Staff Onboard

Once patients come into your practice, be prepared to deal with any disagreements or misunderstandings that may be waiting to arise.

• ***As much as possible, have the same staff member tend to the same patients.*** Dr. Pascucci says this helps create a bond between the patient and the practice. "If one of my techs has assisted Mr. Smith or Mrs. Jones in the past, we do our best to ensure that the same person works with him or her again," he explains. "When a patient sees the same technician at every visit, she develops a relationship and a level of trust. I recently gained a new patient because the practice she previously went to got bigger and bigger, and not only did she see the doctor for shorter and shorter periods of time, she also said she never encountered the same staff member twice; at every visit she was greeted by a new person. She came to feel that she didn't know anyone there, so she decided to find a smaller, more personal practice. A friend recommended our practice for that very reason."

• ***Make sure all your technicians can answer a wide array of patient questions—and make sure their answers will match yours.*** "Their answers should be scripted," notes Mr. Pinto. "That way, the answers they give to patient questions are always the same answers the patient would receive from the provider."

Dr. Pascucci agrees, noting that it's important for staff members to get their question-answering information from the doctor rather than from a consultant or by attending meetings. "If you take your staff with you to meetings and let them listen, they'll be picking up someone else's viewpoint and prejudices," he notes. "For example, they may end up favoring or disliking a specific lens or treatment approach. It's more useful to encourage them to listen to what you say to your patients. If there isn't enough time for your techs to be in the exam room observing and listening, this should be dealt with after the patient leaves. In our practice the staff is encouraged to ask what I recommended and why. Over time they become quite knowledgeable, and their knowledge is consistent with mine. That means that regardless of which staff member a patient asks about something, the answer will be the same."

• ***Consider hiring a lay educator***. "If your practice draws in many patients who are better educated and/or more argumentative, one solution is to allow more time to manage such patients. However, that's tough in the current economic climate," notes Mr. Pinto. "An alternative is to have a high-functioning lay educator in the practice who can step in when patients are taking up a lot of time. You can personally answer the first couple of questions, and then turn the patient over to your educator for questions #3 through #45. It's not uncommon for

practices with a large surgical volume to have a surgical counselor serving as a patient educator.

"You have to arrange to deal with whatever kind of patient population you have," he adds. "To use a metaphor, if you practice where the snow falls, you'd better have a snow shovel. If you practice where the patients are really smart and well-educated, or disputatious—parts of New York come to mind—then you're going to have to be prepared to answer questions personally or through a proxy."

• ***Learn from your experience in other settings.*** Because a pleasant experience in the waiting room helps to diffuse anger, it pays to be open to new ideas about how to accomplish that. "When you go to the gym, the spa, the car dealership or the retail store, notice what they do to make you comfortable," suggests Mr. Pinto. "You'll come away with ideas for what you can add to your own clinic to make it a more pleasant experience for the patient, and ultimately make the patients more pleasant to be with when they're in the exam room."

Dr. Thompson agrees. "About 10 years ago we assembled 10 physicians from different practices under the direction of Jim Gilmore and Shareef Mahdavi, and began meeting periodically in different cities like Chicago, Cleveland and Washington, D.C.," he says. "We spent time going into places that create a great customer experience, like the American Girl Doll store in Chicago. Then we'd go back to our meeting room and discuss what we'd learned and how it could be applied in our practices. We did this for two years, and we learned a lot about creating a great patient experience."

Managing Confrontations

Despite your best efforts, some patients in some circumstances will end up in conflict with you or your staff. These strategies will help keep things under control:

• ***Have a practiced way for everyone on staff to respond to an upset patient.*** Mr. Pinto notes that doing a good job of managing difficult patients doesn't just make work a lot more pleasant—it also prevents lawsuits. "As they say in malpractice insurance circles, patients don't sue because of bad outcomes, they sue because of bad relationships," he says. "Your practice should have a plan for how to respond when a patient is unhappy with a result. That way a bad mood or high stress level on the part of you or your staff won't lead to a negative encounter."

> **"There's no shame in seeking assistance from a counselor or industrial psychologist."**
>
> —John Pinto

Should the staff receive special training in managing difficult patients? "I prefer not to delegate this sort of thing," says Dr. Pascucci. "The staff will be given the psychologist's viewpoint on everything, which may or may not agree with my viewpoint. So I choose to teach my staff how I would like them to behave when faced with a difficult patient. I got a lot of my ideas about how to manage this from reading a book about how the Ritz Carlton hotel trains its staff: *The New Gold Standard* by Joseph Michelli. In fact, one of our receptionists used to be the front desk manager of a nice hotel here in Naples, Florida. She treats our patients the same way she treated the hotel patrons. She says: 'It will be my pleasure. Absolutely. No problem.' Now, the rest of the staff has started talking the same way. They don't want to seem less polite than her."

• ***Remember that your staff will take their cue from you.*** Dr. Pascucci points out that the doctor's example makes a big difference in how staff behave. "In general, the older staff members are better at managing upset patients than younger staff members, who tend to get frustrated," he says. "But I believe that overall, the staff members take their cues from the doctor. If the doctor displays some degree of patience and manners and understanding, the staff will follow suit."

• ***When you disagree with a patient, make sure to explain your reasons.*** "If you agree with the patient's preconceived notion, tell him so; if you disagree, give him a reason," says Dr. Pascucci. "Patients need to perceive your thought processes as being well-thought-out, logical and based on experience."

• ***Break up a challenge by conceding the possibility that the patient may be right.*** "Whether you're a provider or a staff member, when a patient has asked his fourth question or is trying to argue medical wisdom, the universal solvent is to politely say, 'You know, you might be right.'" That quiets him down and allows him to listen to whatever you say next, which might be: 'However, the evidence in our practice experience has been that X is actually the case.' Or: 'However, things have worked out very well for the past 1,000 patients we've provided this procedure to.' That will allow you to foreshorten the discussion."

• ***If you often have a problem dealing with patients, have a staff member serve as a go-between.*** "If you're the kind of doctor who is a great surgical technician but not so great with personal relationships, try to interpose a lay staff member between you and the patient—someone who can soften your touch," says Mr. Pinto. "I have plenty of surgeon clients who really don't like patients all that much. They adore surgery, they love medicine, they love solving patient prob-

lems, but they don't like dealing with the human being behind that pair of eyes. So, they have staff members act as a lubricant between the patient and the cranky doctor."

• ***Consider making yourself available via email.*** "I give every patient my personal email address, so if they have any questions preop or postop they can email me," says Dr. Thompson. "All of my exam rooms have a stack of my business cards. It's amazing how many of my senior patients email me. At the same time, abuse of this has been almost nonexistent."

• ***If you need counseling assistance, get it.*** "The doctors who tend to get the most exasperated by difficult patients are those who are very insecure," notes Mr. Pinto. "A self-assured, confident doctor is never defensive when a patient second-guesses his judgment or says 'What about this medication or this treatment?' It's the doctors who are less secure professionally and thus more defensive who can spiral up into a tangle with these so-called difficult patients.

"If you bristle when a high-school-educated patient says, 'Gosh doctor, I'm not seeing as well out of that eye you operated on as I thought I would,' you probably would benefit from counseling," he continues. "Some doctors become defensive easily, whether it's when their 9-year-old daughter argues with them, or a shopkeeper asks about their motives or a patient or staff member asks a question that appears to defy their authority. If you feel a little tense when someone does that to you, that reflects a sense of insecurity. It's very reasonable to ask yourself why that's the case. If this is a frequent experience, it's likely that you have an issue, not your patients.

"There's no shame in seeking assistance from a counselor or industrial psychologist," he adds. "The assistance they provide might help you enjoy your work a lot more, as well as lowering the stress level in your practice. Industrial psychologists working in health-care settings tell us that, as the physician, you have a lot of control in regards to how you respond to patients who are difficult or challenging. If you find yourself uncomfortable with how reactive you are when patients challenge you, it's really a great kindness to the rest of your professional life to make sure that you get some insights from that. Any qualified counselor, and certainly any industrial psychology expert, can help. Ultimately, they can help you turn that frustration into a kind of game in which you sort of parry and thrust in response to whatever the patient is coming at you with."

Making the Best of It

For a doctor in the 21st century, there's no escaping the occasional encounter with a difficult patient—and the likelihood of that encounter does seem to have increased with the explosion of information access and increased expectations of instant gratification that have come with it.

"It's a great frustration that in these days of tapering fees, rising costs and falling profits, we simultaneously have to up our game and provide better objective outcomes, as well as create better subjective impressions for our patients," says Mr. Pinto. "But that's the name of the game. And it's not just happening in ophthalmology; it's happening at every level. People have much higher standards today for restaurants and haircuts and hotel rooms. They have more options to choose from than every before. So we have to up our game accordingly."

"This is a tough job," adds Dr. Pascucci. "Many doctors who have been doing this for a long time are burnt out. But having an effective strategy for managing difficult patients can do a lot to lower the stress and make the work more palatable." REVIEW

1. Diaz JA, Griffith RA, et al. Patients' use of the Internet for medical information. J Gen Intern Med 2002;17:3:180-5.

Finding Happiness Amidst the Chaos

Michelle Stephenson, Contributing Editor

Here's how to cope and remain focused on patient care during stressful times.

The practice landscape is quickly changing. From health-care reform to electronic medical records to high expectations from patients and third-party payers, stress among physicians is at an all-time high. "The chaos that physicians are feeling comes from the rate at which change is occurring," says Craig N. Piso, PhD, president of Piso and Associates, and a clinical assistant professor of psychiatry at the Commonwealth Medical College in Scranton, Pa. "It can be difficult to adjust to change. Even though many of these stressors are in the world of the imagination or assumption, it's enough to get physicians really stressed out."

He recommends staying focused on the fact that the jury is still out on most of the issues surrounding health-care reform. "Don't make assumptions or believe the rumor mill," Dr. Piso says. "Wait until the changes actually take place to become worried. However, be proactive. Take steps now to be frugal in your practice, assuming that threats could be real, but don't torment yourself by believing it's a done deal before it's a done deal."

These new stressors are compounded by the issues that physicians have always faced. "Taking care of people who are sick and scared can, in and of itself, be stressful," says Matthew Goodman, MD, co-director of the University of Virginia School of Medicine's Mindfulness Based Stress Reduction Program. "Additionally, in the past 10 or 15 years, there has been an increased focus on productivity, so there is more pressure to see more patients in a shorter period of time, and I think that just compounds the basic problem of having a job that can be inherently stressful. Additionally, there are high public expectations."

Stress at work doesn't just affect your work life. It can infiltrate all areas of your life. "When we become distressed and are not coping well, there is a tendency to become fearful or anxious and regressive—to become more preoccupied with ourselves and our state of insecurity. This will have a broad effect that will spill over both at work and in our personal lives," Dr. Piso says. When people become stressed, they tend to become self-absorbed. Instead of focusing on patients or their relationships with family members and friends, they begin focusing on themselves. "While this is normal, it is extremely unhelpful for running a successful business or managing a successful life," he adds.

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Remain Focused on Others

To prevent self-absorption, Dr. Piso recommends maintaining a focus on a mission and on a purpose greater than oneself. "As physicians, that means taking care of patients, which is the best way to ensure business success," he says. "Really treat them exceptionally well and wow them through both medical/surgical treatment and customer service. Do the same thing with staff, because you don't succeed in business without your staff representing you and enabling you. The purpose that is greater than oneself is serving the mission of patient care, the organization that you are a part of, your staff and their families, and then trusting that, by being mission-focused, it comes back to you," he says.

This helps in several ways. When you are thinking about others, you are at least temporarily not thinking about your own problems or worries. Additionally, if one of your worries is the future success of your practice, maintaining an outward focus can be good for business. "It is the most important business strategy," Dr. Piso says. "Also, really empower your staff, who in turn take care of these patients and take care of you. It comes back to you many times over when they see that you are an unselfish leader. You are modeling the highest-level behavior that you would want from staff."

Change your Mind-set

Another way to cope with change is to learn to embrace it, which can be difficult for some people. "This may be the most important thing," Dr. Piso says. "Healthy, strong individuals, in general, become really adaptive and flexible. There are things people can do to develop emotional core strength. This allows them to gain better ability to make adjustments, to be adaptive and to be flexible. We know that if you have rigidity at a time when you are required to be flexible, you're going to have your rough edges polished or beaten off of you. It can be rough going for those who do not embrace change. The ones who are going to thrive are the ones who say, 'Bring it on!'

"Rejecting change just doesn't fly," he adds. He quotes the author Stephen Covey, "What we need in this world of permanent white water is something that does not change—a changeless core." If you have core strength and you are solid and strong at the center, you can be open, adaptive and flexible when it comes to dealing with the changes occurring outside of you, Dr. Piso says.

Strategic Planning

While there are some things you can't change, there are many things that remain within your control. Instead of worrying about the future, strategically plan a future course for your practice. "Say that in the next year, two years or three years, at a minimum, this is where I want to be in my practice," Dr. Piso says. "Think about things like the number of providers you want to have, the provider mix, the types of services you will be offering, the geographic scope, and when and whether you want to add more partners. Those who have a strategic plan and answer some of those key questions are going to cope much better amidst the chaos and the changes coming down the pike than those who become reactive like a weather vane in a swirling wind. Be the wind. Determine your own direction. Have a plan. Be proactive. In the future, you might have to adjust and recalibrate, but at least you are polishing an existing plan as opposed to swirling in the wind because you have no plan."

Self-Care and Wellness

Especially during times of turmoil and stress, it is important to focus on wellness. While it is important to maintain an outward focus, make sure to take some time to focus on taking care of yourself. People who are stressed or anxious often don't get enough sleep, which can make them more stressed and anxious. "If you focus on sleep, other things tend to normalize a bit, and you are able to cope better with the stressors of your day," says Sara Taylor, MD, a family physician in Alberta, Canada, who is currently working on the Physician Wellness Anthology Project, which promotes physician wellness through sharing personal stories and ideas on dealing with stress. (saratmd.com)

She also notes that eating well is important, even if surgeons feel like they don't have time to eat a healthy lunch. She recommends incorporating it into your routine to bring a healthy lunch from home to keep

> **"The purpose that is greater than oneself is serving the mission of patient care, the organization that you are a part of, your staff and their families, and then trusting that, by being mission-focused, it comes back to you."**
>
> —Craig N. Piso, PhD

you from making unhealthy choices during the day when there may not be time to search for healthy options.

Daily exercise is also important to keeping stress levels under control. "Many workplaces have brought in yoga instructors. This is fantastic and can make a big difference in your stress level," says Dr. Taylor. "Have a room in your practice with some exercise equipment, or try to get outside," she says. She notes that there are even meditation phone apps that can be helpful.

Relaxation and creative outlets are also great stress-reducers. "Read, or just hang out with family," she says. "My blog has allowed me to have a hobby and be creative. I think those things are really important, too. Surgeons may play an instrument or take up writing. Foster hobbies that channel your creativity."

Separate Work and Home

Dr. Taylor recommends compartmentalizing work and not allowing it to filter into your home life. "Find a balance between where work ends and your home life begins," she says. "Technology has made it more difficult to do that. Between computers and handheld devices, you could be doing work all of the time. Charts are electronic. Lab work comes electronically. You really have to separate the two things."

Dr. Goodman agrees. "We now have the ability to be connected 24/7," he says. "I recommend that physicians watch that when they are not working, because much of this connectivity is self-imposed. There are times when we are on-call, and we need to be on-call and connected, but there are times when we are on vacation and the culture should accept the fact that we are not checking e-mail and returning phone calls while on vacation. I think that doctors need to protect their own time and make sure that they take some time for themselves and disconnect from their devices."

He adds that physicians need to make sure that they are not working to the exclusion of maintaining their relationships with their families and friends. He also recommends nurturing a spiritual connection. "This can include formal affiliation with a religion or just having a connection to something greater than yourself, whether it is through yoga, meditation or spending time in nature," he says.

Dr. Taylor also cautions physicians against saying yes to too much. "Learn to say no. Being overwhelmed can cause stress and fatigue, which can lead to burnout," she says.

She also recommends practicing gratitude by thinking of one thing every day to be grateful for. "I believe that gratitude can help you be happy in life. Focus on the good things in life, instead of the things that don't go well," she says.

She also advises surgeons to be mindful and present in the moment. When people are stressed and anxious, they may be so busy concentrating on what's coming next that they miss out on what's happening right in front of them. "When we try to multitask, we may think we are getting many things accomplished, but, in fact, our divided attention does not allow us to do any one thing really well," she warns. "Mindfulness makes you stop and be present in the moment. Whether you are with your children or in an encounter with a patient, just stop and notice how much you are really paying attention. Are you truly in the moment and paying attention to what people are saying?"

Dr. Goodman recommends working to become more self-aware. Learn to monitor your own thoughts and feelings to know when you are becoming stressed, and then learn to calm yourself. "In order to effectively and compassionately care for other people, you have to care for yourself," he says. "If you are burned out and stressed out, it is hard to be your best with patients, both technically and in your relationships. I was recently talking to a nursing colleague, and she told me that, in their guidelines, self-care is considered an ethical obligation. It is interesting to think of it that way, because when we think about self-care, we think it is self-indulgent, but if we don't do self-care, we are at risk for burnout and poor practice, if not malpractice. People who are burned out and stressed are more likely to drop out of the profession all together, and we certainly see that happening with doctors leaving the medical profession at a time when we really need doctors. People might think that they are being good professionals by working themselves too hard, but in a sense they are really not." REVIEW

> **"Find a balance between where work ends and your home life begins. Technology has made it more difficult to do that. … You really have to separate the two things."**
>
> —Sarah Taylor, MD

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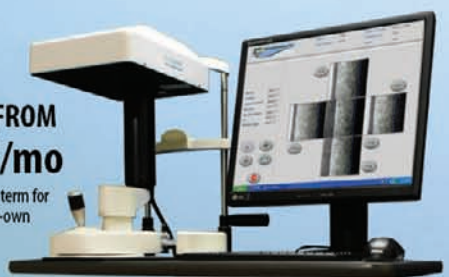

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Ocriplasmin for VMT: A Review of Safety Data

After nearly a decade of use, what the data says about the ocular and systemic safety of these increasingly used drugs.

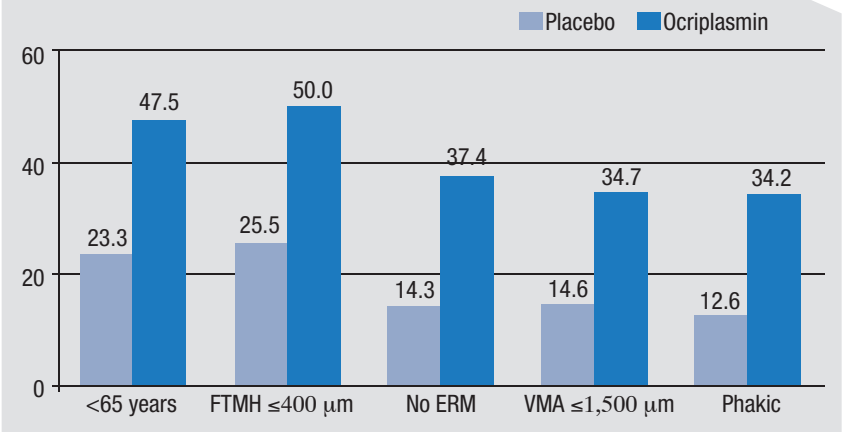
Peter K. Kaiser, MD, Cleveland

Vitreomacular adhesion can progress to vitreomacular traction, a progressive degenerative disease, which results from incomplete posterior vitreous detachment.[1-6] *(Stalmans P, et al. IOVS 2014;55: ARVO E-Abstract 309.)*

Untreated symptomatic VMA/VMT can lead to debilitating visual symptoms and is a risk factor for the development of full-thickness macular holes (FTMHs).[6-11] Ocriplasmin is the only approved pharmacological treatment option for patients with symptomatic VMA/VMT. It is a novel truncated form of plasmin that enzymatically cleaves structural proteins at the vitreoretinal interface, leading to liquefaction and vitreous detachment.[12,13] The efficacy and safety of ocriplasmin was demonstrated by the Phase III MIVI-TRUST Study program that showed that overall, a single intravitreal injection of ocriplasmin (125 µg) resulted in a higher proportion of patients achieving VMA resolution (26.5 percent) at day 28 versus placebo (10.1 percent).

A separate analysis of the Phase III trial data identified positive predictors of VMT resolution at day 28 including absence of an epiretinal membrane, VMA diameter ≤1,500 µm (focal adhesion), presence of FTMH ≤400 µm in width, phakic lens status and age <65 years *(See Figure 1)*.[14] *(Ray S. Independent baseline features predictive of pharmacologic VMA resolution in the Phase III ocriplasmin clinical program. Presented at AAO Retina Subspecialty Day, Chicago, 2012.)*

Figure 1. VMA Resolution at Day 28 by Baseline Predictors



Real-world Experience

Recent reports have confirmed the improved rates of VMT resolution in the real world when following these positive predictors of response *(See Table 1)*. At the Cole Clinic, 47 percent (eight of 17) of our first patients to receive ocriplasmin demonstrated VMA resolution, and 80 percent (4/5) had closure of their FTMH.[15] Patients with absence of ERM and VMA ≤1,500 µm had resolution rates of 50 percent and 62 percent, respectively.[15] At the Retina Institute in St. Louis, 64 percent (14/22) of patients achieved VMA resolution, and 33 percent (one of three) of patients achieved macular hole closure. Experience from the Bascom

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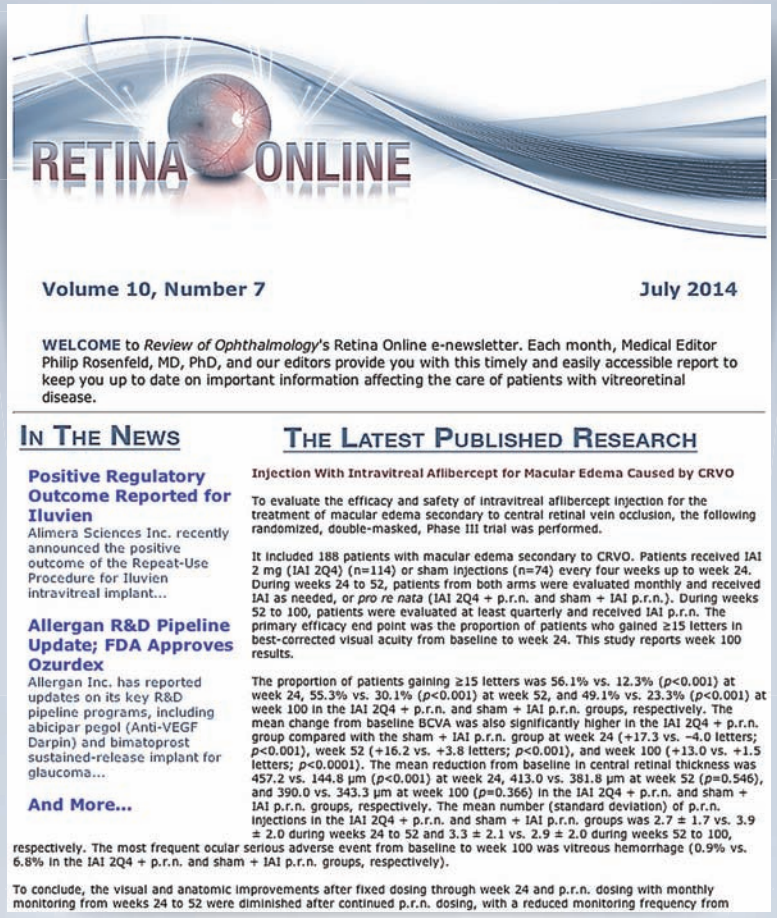

RETINA ONLINE

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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.

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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

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Palmer Eye Institute in Miami showed a total of 33 percent (11/33) of patients achieving VMA resolution, with 36 percent (four of 11) achieving FTMH closure post injection with ocriplasmin. *(Fortun, J. Paper presented at: 17th Annual Club Vit Meeting, June 28 to July 2, 2014. Beaver Creek, Colo.)*

At the Retina Vitreous Center in New Jersey, a total of 41 percent (25/62 eyes) achieved VMA resolution and 48 percent (14/29 eyes) achieved FTMH closure following ocriplasmin injection. *(Roth D, et al. IOVS 2014;55: ARVO E-Abstract 298.)* The California Retina Research Foundation in Santa Barbara reported that a total of 56 percent (14/25) of patients achieved VMA resolution and 36 percent (four of 11) achieved macular hole closure post injection with ocriplasmin. *(Nasir M, Pieramici D, Castellarin A, et al. Paper presented at: The American Society of Retinal Specialists 31st Annual Meeting; August 2013; Toronto.)*

In summary, real world clinical results from these large practices show improved efficacy over the clinical trial results can be achieved with optimal patient selection.

Table 1. VMA Resolution at Day 28 at Different Clinical Sites

	VMA RESOLUTION RATE (%)				Overall rate of MH closure (%)
	Overall efficacy	VMA diameter ≤1,500 µm	No ERM	MH present	
Bascom Palmer	33	37	42	45	36
California Retina	56	n/a	57	73	36
Cole Eye	47	62	50	n/r	80
NJ Retina	41	55***	48	72	48
Barnes	64	n/a	72	100	33

n/a not available
n/r not reported
*** VMA diameter cutoff was ≤750 µm for this group.

Ocriplasmin Safety

Safety data from the Phase III clinical trials demonstrated that ocriplasmin was generally well tolerated when administered as an intravitreal injection, and most adverse events were ocular and mild or moderate in severity.[14] A collection of AEs were identified as adverse events of special interest by the American Society of Retina Specialists Therapeutic Safety Committee based on their clinical relevance. *(Hahn P, et al. IOVS 2014;55: ARVO E-Abstract 2209.)* The ASRS TSC was commissioned to monitor post-marketing drug- and device-related adverse events, utilizing periodic aggregate safety reports consisting of post-marketing reports and clinical trial data. The TSC identified different categories of AEs of interest, which included vision function changes (visual acuity alterations, dyschromatopsia and electroretinogram changes); anatomic retinal findings (retinal/macular edema [preferred term for subretinal fluid] and ellipsoid zone changes); and other safety findings including retinal tears/detachments, lens subluxation/phacodonesis, impaired pupillary reflex and retinal vessel findings *(See Table 2). (Hahn P, et al. IOVS 2014;55: ARVO E-Abstract 2209.)*

Visual Function Findings

The most common visual adverse events from the Phase III clinical trial program were vitreous floaters (16.8 percent) and photopsia (11.8 percent), which are known to be associated with PVD.[14] Blurred vision and visual impairment were also reported in 8.6 percent and 5.4 percent of patients.[14] Acute decreases in visual acuity (defined as >two line decrease) were observed in 7.7 percent of patients during the clinical trial program by day seven. The time to onset was one to two days after injection and had a median time to resolution of 14 days. A total of nine patients from the clinical trial program still had decreased visual acuity at month six, which in most cases was due to VMT or macular hole progression, or stemmed from vitrectomy complications. The reported frequency of visual impairment, according to the second periodic benefit-risk evaluation report for ocriplasmin (PBRER 2) was 1.8 percent, which included the following MedDRA terms: visual impairment; metamorphopsia; scotoma; vision blurred; visual acuity reduced; visual acuity reduced transiently; visual acuity tests abnormal; visual field defect; blindness (transient); visual brightness; halo vision; and loss of visual contrast sensitivity. Dyschromatopsia was noted in 1.7 percent of patients in the clinical trial program and in 0.4 percent from post-marketing experience.[14] Of the seven events with follow-up outcomes in PBRER2, time to onset was rapid at ≤one day with the majority (57 percent) of the cases achieving resolution or resolving. ERG changes occurred frequently with dyschromatopsia. ERG changes were reported in at least half of the dyschromatopsia cases in the pivotal trials (estimated frequency of 2 per-

Table 2. Frequency of Adverse Events of Special Interest

Adverse Event	Pre-marketing Clinical Trial Program Frequency (%) N=1,017	Post-marketing Frequency (%) N=6,909
Acute decrease in visual acuity	7.7*	1.8**
Dyschromatopsia	1.7	0.4
Retinal tear/detachment	0.4***	0.3
Lens subluxation/phacodonesis	two cases reported	one case reported
Impaired pupillary reflex	0.5	0.2
IS/OS findings	NR	0.2
Retinal vessel findings	one case reported	two cases reported
ERG changes	2.0****	three cases reported

NR = not reported
* From Phase III clinical trial program (n=465)
** Includes (but was not limited to) reports of VA decrease
*** From Phase III clinical trial program (n=465), pre-vitrectomy occurrences
**** Overall frequency for ERG changes cannot be calculated as systematic prospective ERG recording was not consistently required in all studies. ERG changes were reported in at least half of the dyschromatopsia cases in the pivotal trials (estimated frequency of 2 percent).

cent) but systematic prospective ERG recording was not consistently done in all studies. ERG changes included decreased a and b wave amplitudes with time to onset of <one week. Only one of the Phase II trials, the MIVI-008 trial, had baseline and post-injection ERGs done in a subset of patients who received ocriplasmin. In this subset of patients who had baseline and post-injection ERGs, five of 13 (38.5 percent) showed abnormal changes from baseline, and all showed resolution by last follow-up. There were three cases of ERG changes reported from the post-marketing experience, with two exhibiting isoelectric responses. *(Ocriplasmin 2nd Periodic Benefit-Risk Evaluation Report. ThromboGenics NV. December 19, 2013.)* Overall, ERG changes were generally transient (median time to resolution of six months) and correlated with dyschromatopsia. *(See endnotes for additional citation information.)*

Anatomic Findings

The visual function changes were also associated with anatomic changes. Outer segment ellipsoid zone (IS/OS junction) changes were not identified during the clinical trial program because time-domain OCT was used, while during the postmarketing period, the reported frequency was 0.2 percent (15 cases of photoreceptor alterations). In our patients, the frequency of this outer retinal change was considerably higher. We saw it in 41 percent of patients. The loss of the OS ellipsoid zone occurred by day five on average with a median time of resolution of 29 days.[15] Subretinal fluid was temporally associated with ellipsoid zone layer disruption. From the Phase III clinical trial program, 5.4 percent ocriplasmin-treated patients had SRF with a median time to onset of eight days. *(See endnotes.)* From a post-marketing study, the SRF average time to onset was 4.5 days and average time to resolution was 30 days.[15] Overall, the ellipsoid zone and SRF changes were transient.

Other Safety Findings

Lens subluxation/phacodonesis occurred in two cases in the clinical trial program and one case was reported during the post-marketing period. Retinal tears/detachments occurred in 1.9 percent of patients in the clinical trial program. Pre-vitrectomy, retinal tears/detachment occurred in two patients (0.4 percent) in the ocriplasmin group and one patient (0.5 patient) in the placebo group. The incidence was 0.3 percent during the post-marketing period. Impaired pupillary reflex occurred in 0.5 percent of patients in the clinical trials and 0.2 percent during the postmarketing period. For the postmarketing cases, the time to onset was 0 to five days with resolution in three cases, two reported to be resolving, three cases reported as unresolved, and resolution status unknown in five cases. The frequency of retinal vessel alterations was low, with only one case reported in the clinical trial program and two post-marketing cases. These findings included retinal vessel attenuation or vasoconstriction. The one clinical program case resolved but the resolution status of the cases from the postmarketing period is unknown and was ongoing at the time of the report. This collection of adverse events was low in frequency in both the clinical trial program and the

post-marketing experience. *(The data presented in this section is from the Ocriplasmin 2nd Periodic Benefit-Risk Evaluation Report. ThromboGenics NV. December 19, 2013.)*

Ocriplasmin is the only approved pharmacological treatment for patients with symptomatic VMA including FTMH. Increased overall VMA resolution rates have been reported from postmarketing experiences at multiple centers. Positive predictors of VMA resolution include focal VMA, presence of FTMH and absence of epiretinal membrane. These baseline characteristics should aid physicians in selecting patients who are likely to gain the most benefit from ocriplasmin treatment. Safety findings were generally consistent between the clinical trial program and the postmarketing experience. While numerous hypotheses have attempted to explain the observed anatomic and functional changes, more investigations are warranted to fully understand the phenomenon. Real-world experience shows the correlation between the anatomic and functional changes and the patient symptomatology. It is therefore important to set appropriate patient expectations about the clinical course post ocriplasmin injection. REVIEW

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3,500 Years of Artificial Tears

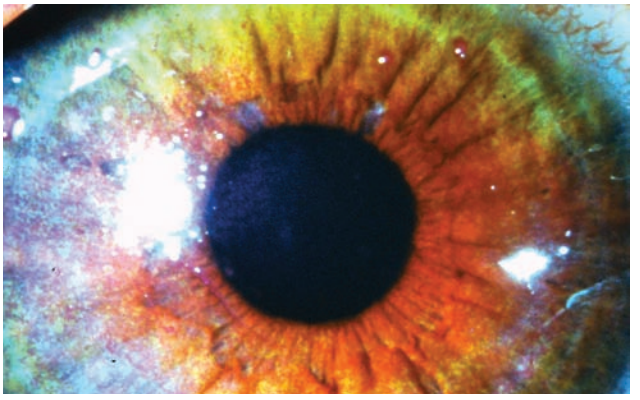
After three millennia of battling the discomfort and irritation of dry eye, is ophthalmology any closer to a solution?

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Ashley Lafond, Andover, Mass.

"If a man's eyes are affected with dryness, he shall rub an onion, drink it in beer, apply oil to his eyes. Thou shalt disembowel a yellow frog, mix its gal in curd, apply to his eyes."

— Prescription from Assyro-Babylonian ophthalmology[1]

Based on the quote above, it seems we've been trying to find relief from dry eye for quite a long time. In 1872, Georg Ebers, a German Egyptologist, discovered a collection of Egyptian medicinal recipes later called the Ebers Papyrus, written sometime between 1553 and 1550 B.C.[2] Eye pastes with exotic elemental ingredients such as antimony, copper or manganese were referenced throughout the document as anti-infectives, sunscreens or cosmetics.[3] We've come a long way since then, but dry eye still remains one of the more challenging diseases to treat. With only one drug (Restasis, Allergan) earning Food and Drug Administration approval to date, we are left with a potpourri of artificial tears to address this unmet need. A visit to any local pharmacy will find shelves of drops, lubricants and gels all offering symptomatic relief for dry-eye sufferers. Although these are not the cures we might hope for, the artificial tears of today are a long way from both the yellow frog gal of ancient Egypt and the saline drops that were the first modern tear replacements. Many artificial tears available today reliably mimic real human tears, and several may actually outperform their natural counterparts. In this month's column, we'll provide an assessment of the current artificial tear landscape, and take a look at how formulations have evolved to optimize hydration and lubrication.



Humans have been battling the signs and irritating symptoms of dry eye as a specific diagnosis for thousands of years.

The Tear Film and Blink

A healthy, stable tear film provides a smooth protective layer over the corneal surface that's essential for good vision and ocular comfort.[4] Conventionally, the tear film is thought to be composed of three layers: an outer lipid layer (~ 0.1 µm thick) produced by the meibomian glands in the tarsal plate; a central aqueous layer (~ 7 to 10 µm thick) produced by both the main and accessory lacrimal glands; and an inner mucin layer (~ 0.2 to 1.0 µm thick) produced by goblet cells in the conjunctiva.[4-7] Recent work has amended this three-layer architecture with the concept of an integrated aqueous and mucin layer. While mucins concentrate close to the ocular surface, a significant amount of mucin, particularly mucin 5A, is distributed throughout

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the aqueous tear film.[5-7] Still, this triple-layer structure remains useful in understanding the multitasking of the tear film and the pathophysiology of dry eye. At the molecular level, the list of components could fill volumes, and includes water, electrolytes, antimicrobial molecules and several peptide growth factors.[7] This is just a small sample of a tear component list that includes many more constituents found in vanishingly small amounts, each playing some role in maintaining a healthy ocular surface. Among these roles are constant hydration of the cornea and conjunctiva; protection of the ocular surface from dust, dirt particles or foreign bodies; and maintenance of corneal transparency for clear vision. Tears also provide a source of nutrients for the avascular cornea. When the quality or quantity of tears is compromised by an imbalance or breakdown in any of these components, it can severely impact the eye and cause or exacerbate dry-eye symptoms.[5,6]

The tear film is not a static entity, but rather is in a state of constant flux, with each blink forcing a fraction of the total volume out through sinus canalicular drainage to be replaced by lacrimal, meibomian and goblet cell secretions. The tear film's life cycle spans the time between two blinks, and its deterioration and eventual breakup initiate the next blink. Measuring tear-film breakup time, visualized with fluorescein, is a standard assessment of tear-film health. A more integrative assessment of the tear film used in clinical research, called the ocular protection index, is a ratio of blink rate over breakup time.[8] Ideally, blinks replenish a healthy tear film prior to significant breakup, and an unstable tear film can prompt blinking at a faster rate, one of the known consequences of dry eye. The OPI score reflects this anomaly: in a subject with an OPI < 1, breakup time is shorter than blink rate, leading to an exposed, compromised ocular surface. Conversely, a subject with an OPI score > 1 reflects a healthy tear dynamic where blinks precede the breakup of the aging tear film.

Dysfunction of any component of tears can lead to tear film instability, ocular surface exposure and dry eye. Inadequate lubrication results in ocular surface damage, discomfort and compromised visual function, all of which can negatively affect the patient to varying degrees, often drastically reducing quality of life. Many external and internal factors play a role in the development or exacerbation of dry eye. Visually intensive situations like working on a computer, reading or driving at night can contribute to a hyper-stressed tear film as the blink rate is reduced by concentration. Certain medications, systemic diseases, contact lens use, ocular allergy, refractive surgery, age and gender are also risk factors for the disease. In order to supplement a deficient tear film, tear substitutes are commonly used as a first line of defense.

The Challenge

Current prevalence of dry eye in the United States has been conservatively estimated at somewhere between 6 and 10 million people;[9] other projections suggest as many as 11 percent of adult men and 17 percent of adult women are affected.[6] These rates will undoubtedly grow in the next 10 to 20 years as the population ages. As the mainstay of therapy for dry eye, the artificial tear market is projected to reach $2 billion globally by 2018. This is not the result of a blockbuster success story, rather it's a reflection of the failure of any single product to provide relief for more than a fraction of dry-eye sufferers.[7]

One of the most significant challenges for all topical products is that they are rapidly eliminated from the ocular surface by a variety of barrier functions. Even when tear function is compromised, newly secreted tears are still acting to dilute and wash away active agents from added drops, while blinking exchanges the existing tear film and removes instilled tear substitutes by continuously pushing the tears into marginal menisci and punctal openings. Finally, the sensitivity of the cornea to minute changes in pH and osmolarity resulting from eye-drop instillation induce reflex blinking and tearing, further preventing a therapeutic benefit from artificial tears. We see that any artificial tear fights an uphill battle with regard to residence time. The key challenge is to develop a formulation that would remain longer on the ocular surface and thus provide a more sustained therapeutic effect.

When posing the question of what makes a good drop, the symptomology of dry eye provides a checklist of therapeutic targets. Drops should reduce burning, improve reading speed and comprehension and normalize blink pattern and frequency. These are all factors that our patients will perceive, and even if they can't identify the specific effects of the drops, we can quantify the changes in the clinic and use them as a guide in eye-drop development. An example of this is the inter-blink interval visual acuity decay test. The decline in acuity measured with IVAD is greater in those with dry eye than normal controls, but it can be normalized with artificial tears.[10]

Generations of Artificial Tears

Over the years, we've seen many artificial tears come and go on the market, often calling themselves a "next-generation" product. The modern history of artificial tears can be traced back to the days of the traveling medicine show with a product Collyrium, a word that literally translates from Latin as "eye wash." The notoriously famous cobalt blue glass bottle, equipped with an eye-cup top, was designed to make users' "eyes right" by relief from strain or irritation by dust or wind. The eye-

cup bath was a popular delivery system for instilling liquid medications onto the eye until the more traditional screw-capped tops emerged. These early attempts at dry-eye relief were followed by a generation of tear substitutes that were saline-based, isotonic or hypotonic solutions with preservatives, notably benzalkonium chloride. Generally speaking, these artificial tears spread poorly across the ocular surface and their short retention time led to transient relief and very high frequency of instillations.

Jump ahead to the 1980s, and there came a boom in the advancement of artificial tears. This next generation integrated natural polymers (e.g., methylcellulose derivatives) and synthetic polymers (e.g., polyethylene glycol, polyvinyl alcohol, povidone, carbopol, polyguar and HP guar) into artificial tear formulations. All these polymers added a higher viscosity, offering a better retention time than preceding components, and are still included in products like Systane (Alcon) and Refresh Optive (Allergan). The drawback to some of these gel-forming drops is that the improvement in symptoms was at times accompanied by a transient visual blurring. These products also introduced the concept of gentler preservatives or even preservative-free tears, giving patients with sensitivities or allergies additional options.

Hyaluronic acid tears are considered to be the third generation of dry eye artificial tear therapy. HA is a naturally occurring polysaccharide in the human body. While it is found mainly in connective tissue, it is also highly concentrated in the vitreous, and in the aqueous humor where it coats the corneal endothelium. Products such as Blink Tears (Abbott Medical Optics) are set apart by their hyaluronic acid content. The viscoelasticity of the polysaccharide leads to increased tear stability, reduction of tear removal, protective effects on the corneal epithelium and consequently, a reduction in many dry-eye symptoms.[11-13] Still, the viscoelasticity of HA-based products varies significantly, depending on molecular weight and HA concentration. Covalently crosslinking HA generates a more viscoelastic material in comparison to original HA-based tear supplements that have a low concentration of high-molecular-weight HA. One study found that the cross-linked HA applied t.i.d. significantly improved ocular surface health compared to a standard HA-containing tear in dogs with a clinical diagnosis of dry eye.[14] A second study comparing the *in vivo* efficacy of several ocular lubricants in rat and rabbit animal models of dry eye found that 0.3% sodium hyaluronate had a significantly longer retention time than other lubricants, including carboxymethylcellulose and hydroxypropyl methylcellulose.[15]

It's not surprising in light of this discussion that one of the top complaints of patients is that artificial tears don't last long enough. The main benefit of the latest generation of tears addresses this very issue. Most recently, we've seen the introduction of lipid emulsions into the artificial tear arena. Considered the fourth and most advanced generation of artificial tears, lipid oil-in-water nano-emulsions have been shown to have a long residence time on the tear film, reduce the tear evaporation rate and have a positive effect on the lipid layer.[16,17] Nano-emulsions also improve ocular bioavailability of lipophilic or poorly water-soluble drugs.[18] Generally emulsions need "surface active agents," or surfactants to stabilize them, which commonly create a negatively charged preparation. Several emulsion-based products exist on the market to-date, including Soothe XP (Bausch + Lomb) and Systane Balance (Alcon). Retaine (Ocusoft) is a unique preservative-free artificial tear option containing a proprietary cationic oil-in-water nano-emulsion with novel bioadhesive properties. It's thought that electrostatic interactions between the positively charged oil nano-droplets and the negatively charged ocular surface epithelium increase the residence time on the ocular surface, thereby enhancing the protection and restoration of a healthy tear film and corneal epithelium.[17,18]

Beyond Eye Drops

While it seems that artificial tears will always be a feasible first line of defense for dry-eye sufferers, there continues to be a push for alternative options. Several recent studies focus specifically on one aspect of dry-eye disease: lacrimal gland dysfunction. One of these involves restoration of lacrimal function by transplanting (or, in the case of the parotid gland, rerouting) minor salivary glands, but these procedures yielded a hypo-osmotic tear composition and subsequent epithelial edema.[19] More recent studies have examined development of bioengineered tear-forming glands. In a mouse model that mimics the ocular surface damage of dry eye, duct integration of an orthotopic engraftment of a bioengineered lacrimal gland germ into an adult extraorbital gland-defect model mouse indicated that the bioengineered lacrimal gland replacement can restore the physiological functions of the lacrimal gland, including the production of sufficient volume of an appropriate tear and protection of the ocular surface.[20]

A second strategy aimed at enhancing lacrimal gland function employs autologous platelet-rich plasma. While serum has been used to supplement topical treatments in the past, this new strategy employs PRP *in situ*, liberating a host of biologically active proteins, promoting cell recruitment, growth and differentiation. The technique has been used successfully for treatments including wound closure, corneal ulcers, chemical burns and skin rejuvenation. Beneficial effects have been observed for epithelial re-

covery in post-LASIK corneas and in severe dry eye.[21,22] A recently published pilot study in patients with severe lacrimal dysfunction and dry eye showed that lacrimal injections of PRP were found to be safe and effective in increasing lacrimal production and in reducing ocular staining.[23]

These experimental strategies are likely to be used only in the most severe cases of dry eye. For the majority of dry-eye sufferers, topicals such as artificial tears will continue to be the treatments of choice in a cost-benefit based therapeutic landscape. Still, with the improvements in today's artificial tears, there's no doubt that dry-eye patients are seeing greater choices and more effective products than those of generations past. We've seen that we can do better than yellow frog gal but we also know that there's plenty of room for more progress, particularly in the area of agents that provide greater relief for moderate to severe dry eye, as well as those that provide a greater duration of relief. After 3,500 years of being in the works, the thought of long-term relief for dry eye seems like a therapy whose time is long overdue. REVIEW

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Is Your Anti-hypertensive Treatment Working?

It's tempting to decide whether or not our treatment is working at the first post-treatment visit—but that could be a mistake.

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One of the challenges faced by a clinician treating glaucoma is deciding whether the treatment you've chosen for a given patient is having enough of an effect. While this sounds like a simple enough task, it's actually not simple at all.

The reason answering this question isn't easy is that intraocular pressure is highly dynamic and variable, even without any perturbation of the system resulting from the addition of a medication. In both normal and treated eyes, IOP can change as much as 4 to 5 mmHg over the course of a day. In untreated glaucoma patients, the standard dogma is that pressure fluctuates between 6 and 8 mmHg over the course of a day. If a change of that magnitude were ascribable to medication, it would be a significant and relevant response. And therein lies the problem: If someone can go from 26 mmHg to 19 mmHg on their own, and you start a medicine when they're 26 and they come in and they're 19, how do you know if that change was caused by the medicine?

A similar problem arises when a patient new to our office is already using a glaucoma medication. In that situation, we have to begin by determining how well the current medication is working. If we have documentation of several pretreatment and on-treatment measurements in the patient's records, we can figure out whether or not the primary therapy is doing its job. But if we don't have access to records stating what the patient's pressure was before treatment, then we have no idea how effective the medication is. We only know what the pressure is with the patient on the medication. That doesn't tell us how well it's working.

The Monocular Drug Trial

The monocular drug trial was proposed as a way to determine whether our treatment is doing what we want it to do, taking into account spontaneous IOP fluctuation. For example, if both eyes are 26 mmHg, you can treat one eye but not the other. Then, when the patient comes in next time, the change in the untreated eye will tell you what the spontaneous IOP fluctuation is; the change in the treated eye will be a combination of spontaneous and therapeutic IOP change. If you subtract the change in the untreated eye from the change in the treated eye, then you're subtracting out the spontaneous component, and you should be left with the therapeutic effect caused by the medication. You're basically using the fellow eye as the control eye for the treated eye. This idea sounds great: It's elegant, simple, safe, free and only requires one extra office visit.

The problem is, it doesn't actually work. That's because a lot of things have to be true in order for it to work, and none of those things have turned out to be true. For instance:

• ***Both eyes would have to fluctuate symmetrically.*** If you're going to believe that the untreated eye tells you about the treated eye, then you have to believe that they spontaneously fluctuate up and down together. The data does not support that. We published a paper almost a decade ago categorizing the occurrence and frequency of asymmetric IOP fluctuations, where the IOP fluctuates significantly more in one eye than the other.[1] We found that this is very common in treated glaucoma patients, as well as in normal subjects.

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Robert Weinreb, MD, also looked at left vs. right eye fluctuations using his own (arguably cleaner) data; he also found that there was poor correlation between the two.[2-4]

• ***Pressures measured at the same time of day would have to be fairly consistent.*** We know that there can be a huge intraday change in IOP, so we try to neutralize that by doing our IOP check at the same time of day when we start the medicine and when we bring the patient back a month or so later to assess its efficacy. The idea is that if we standardize the time of day, we minimize the diurnal component in IOP variability. That would make sense if IOP fluctuation follows the same rhythm every day.

This is another assumption that has turned out not to be true. We conducted an NIH-funded study to evaluate this.[5,6] We brought in glaucoma patients and healthy subjects and checked their pressure every two hours from 8 a.m. to 8 p.m. on five different days over the course of a year to see whether their IOP rhythms were conserved from day to day. In fact, they were not conserved in either treated glaucoma patients or in normal subjects. In other words, what your pressure does today does not adequately characterize what it does on other days.

• ***The medicine would have to work as well in one eye as in the other.*** Our group and other researchers have done studies looking at this, and the data shows that there is actually fairly poor correlation between the IOP responses of fellow eyes to the same meds.[7]

• ***There would have to be no crossover effect.*** If one believes that the untreated eye is displaying purely spontaneous IOP variability unaffected by the therapy, then the medicine put in the treated eye can't be lowering pressure in the other eye. That would throw everything off.

For the most part, this is not an issue with prostaglandins because they're rapidly metabolized once they're systemically absorbed. But that's not true as soon as you get into adjunctive therapy and add beta blockers. It's well-known that beta blockers have a significant crossover effect, on the order of 1.5 to 2 mmHg in the other eye.[8] So that's 1 to 2 mmHg of medication effectiveness that gets masked if you do a monocular drug trial with a beta blocker.

For most patients, 30 days without medication is unlikely to lead to clinically relevant progression.

• ***The patient would have to be following your directions.*** Patients are notorious for not following instructions. If they have trouble putting drops in both eyes the way we ask them to, what are the odds they'll remember to only put the drop in one eye, and do so on schedule?

The Proof in the Pudding

Given all of these reasons to doubt the validity of monocular trials, we decided to conduct a retrospective study of a monocular drug trial to see if it worked. The question we asked was: Does the reduction that we see in the trial eye predict the IOP response in the fellow eye when we treat it? The answer was no.[9] Others have replicated that study as well, probably a dozen times now.

The idea that monocular drug trials don't work was not well-received at first. Since this was hard for many clinicians to believe, we decided to conduct a prospective, randomized, investigator-masked study of a monocular drug trial. It also occurred to me that asking whether the treated eye predicts the IOP in the fellow eye was asking the wrong question. The real question is: Does the monocular trial predict long-term response to that medication? So, we set out to try to answer that question.

In this study, one eye was randomly assigned to treatment. The study personnel assessing IOP at baseline and on treatment were masked as to which eye was being treated, and we did three pretreatment measurements and three on-treatment measurements going out to six months to determine the mean IOP change. The difference between the pretreatment mean and the on-treatment mean was our gold standard; that told us how well the medicine worked long-term. So, we looked to see how well the monocular trial predicted that. The answer was: very poorly.[10]

Again, this outcome was not well-received by clinicians, many of whom had come to rely on monocular drug trials to evaluate the efficacy of their treatments. So at this point, the Ocular Hypertension Treatment Study investigators decided to analyze their data to see whether or not they agreed. They had initiated treatment in their treatment group using the monocular drug trial, and they had multiple pretreatment and on-treatment pressure readings. So they were able to perfectly recapitulate our methodology in an *ad hoc* analysis of their OHTS database.

They found exactly what we found.[11] And after our paper and the OHTS paper came out, the monocular trial finally fell out of favor.

Making the Decision

Evaluating the impact of your treatment is crucial to helping your

patients—and I suspect that a lot of medications are not, in fact, helping patients as much as their doctors think. But if a monocular drug trial won't give you the information you need, how do you decide whether the medicine you've prescribed is working?

Our group is trying to answer that question. With NIH funding, we've conducted an evaluation of numerous candidates—clinical tools that might provide better short-term estimates of long-term IOP reduction than the monocular trial does. At this point, we're analyzing the data from that trial, so an evidence-based answer is still in the offing. (We hope to publish our findings with the next year.)

In the meantime, the gold standard is to get multiple pretreatment measurements so you have a reliable idea of where you're starting from; then, get several on-treatment measurements to characterize the efficacy of the newly added IOP lowering therapy. This is not as easy as conducting a monocular drug trial, but there's no shortcut at this time.

Here are a few strategies that will help ensure you make a good decision:

• ***Don't be afraid to have a washout period.*** If a patient comes in already on therapy and past records are not available, it's entirely reasonable to have a washout period and reestablish the pretreatment baseline on at least two occasions before restarting therapy. That will allow you to assess whether or not the patient is getting benefit from the primary therapy. I would avoid doing this in those few patients who have advanced glaucoma—i.e., advanced cupping and visual field loss encroaching within the central 10 degrees. But for most patients, 30 days without medication is extremely unlikely to lead to clinically relevant progression.

Of course, a washout period isn't necessary if you have data from the previous provider that you're comfortable with—data that clearly documents pretreatment IOP, taken using a tonometer that you trust, and with more than one baseline pressure measurement. In that situation it's entirely reasonable to operate on the assumption that you know the real baseline pressure.

• ***If you can get previous medical records, do so.*** However, specify that you want the original disc photos, not a copy. Unfortunately, it's not uncommon to have new patients arrive without their medical records. It's not on most people's to-do list to tell their doctor that they're moving when they relocate. I'm happy to forward a patient's records, but if one of my patients moves away, I may not even know until he fails to show up for three appointments in a row.

When you're the one taking on the patient, it's always worthwhile to formally request the release of previous medical records. Those records are a gold mine, and not just for baseline IOP information. On the records-release form I specifically ask for all clinic notes, all visual fields and any imaging or disc photos that were acquired. The disc photos are particularly valuable, but the person forwarding the records will sometimes make a photocopy of them and send me the copies. Photocopies are totally worthless. To avoid that, I often put in parentheses: "Please send me the original disc photos; I will return them to you at your request."

• ***Resist the urge to switch medications on the first post-treatment visit.*** If a new patient starts at 26 mmHg and then comes in at 24 or 25 mmHg after using a prostaglandin for a month, it's very tempting to conclude that the patient didn't respond to the prostaglandin, and therefore switch the patient to your next favorite first-line agent in a different drug class. However, there's a reasonable chance you're wrong; the patient may have responded but had an IOP fluctuation that masked the response. So you really owe it to the patient not to write in her chart: "prostaglandin non-responder." If you do, you've denied her the most effective, safest and most convenient class of meds available—and possibly erroneously. She'll have to go on to less safe, less effective, less convenient therapy.

Before you do that, get at least one more on-treatment pressure check a week or two later. (If you get wildly different measurements the first two times, a third might help you decide which measurement was more likely the fluctuation.) If the medication truly isn't working, the patient will almost certainly not be any the worse for wear.

At this point, all we can say for sure is that we have not yet optimally characterized the proper frequency and timing of IOP measurements necessary to characterize pretreatment and on-treatment IOP. However, it's definitely more than one measurement.

So: Add or Switch?

Suppose a patient comes in with a pressure of 30 mmHg, and my target pressure is 13 mmHg. If I didn't have existing records, I'd begin by taking multiple pretreatment measurements to ensure that this is the real baseline pressure. Then I'd start him on a prostaglandin. If he returns and his IOP is 26 mmHg, and that is confirmed by a second measurement a few weeks later, this patient only got 4 mmHg from the treatment. Some clinicians might add another drug, but that outcome is far less than I would expect from a prostaglandin, based on the results of studies that characterize its IOP-lowering profile. Rather than add a second medication, in this situation it might be worth discontinuing the prostaglandin and switching the patient to a different

class of drug. (I'm all for switching to another drug class instead of reflexively adding another drug in a situation like this.)

On the other hand, suppose the patient returns and two consecutive measurements show that his new pressure is 20 mmHg. Some clinicians might see that as too far above the target of 13 mmHg and try switching to another medication. However, that's a reasonable pressure drop to expect from a prostaglandin, and if you need a 17-point drop in pressure, no single medication is going to give it to you. So if the drug was tolerated and I got that significant a change, I'd continue the prostaglandin and add something else. The prostaglandin is doing all it can; it just needs a little help to reach the target pressure.

The reality is, any given medication may not be working as well as we think, or it may be working better than it appears to be working at the first on-treatment exam. As clinicians, we rarely worry about whether our measurements are really telling us what we think they're telling us. As a result, it's very tempting to keep adding medications until the in-clinic measurement is low enough to meet our target. But to truly help our patients, we need to make sure we have an accurate pre-treatment baseline pressure, and then check the reliability of the first IOP measurement on the drug by taking a second measurement. That will give us a much better reason to conclude that a drug is working—or conclude that it isn't working and convince us to try something different. REVIEW

Dr. Realini is an associate professor of ophthalmology at West Virginia University Eye Institute in Morgantown.

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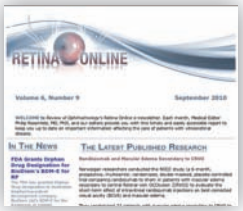

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What Patients Think of LASIK

The results of several well-designed, prospective LASIK studies are shedding light on the procedure's postop pros and cons.

Walter Bethke, Managing Editor

The results of several recent studies into LASIK outcomes were presented at the recent meeting of the American Academy of Ophthalmology, giving surgeons insights into patient satisfaction after the procedure as well as how LASIK's outcomes stack up to traditional methods of vision correction such as contact lenses and spectacles. Here's a look at these studies' results with commentary from the researchers involved.

The FDA LASIK Study

In 2009 the Food and Drug Administration, National Eye Institute and Department of Defense began a study aimed at better understanding the risk for severe complications after LASIK. The effort, known as the LASIK Quality of Life Collaboration Project, consisted of surveys administered to military personnel receiving LASIK (n: 262) as well as to civilians undergoing the surgery at five U.S. sites (n: 312). The follow-up was three months.

In the military arm, called Patient Reported Outcomes with LASIK-1, the mean preop spherical equivalent error in the myopic eyes was -2.9 D. The mean in hyperopes was +2.5 D. In the civilian study group, designated PROWL-2, the mean SE in myopes was -4 D, and the mean in the hyperopic eyes was +2 D.

At three months, looking at both groups, at least 95 percent of patients saw 20/20 or better. Only one eye (in PROWL-1) lost two or more lines of best-corrected vision.

Patient satisfaction results were high in both arms of the study. "In PROWL-1, 99 percent of patients were satisfied with their outcome and in PROWL-2, 96 percent were satisfied," avers Edward Manche, MD, a PROWL-2 investigator and the director of cornea and refractive surgery at the Stanford University Eye Laser Center. "There's been some meta-analysis in the literature and this really goes along with what that analysis has found."

In presenting the study, two of the organizers' focal points were visual symptoms, such as glare and halo, and dry-eye disease. Though the prevalence of visual symptoms overall didn't increase postoperatively, a percentage of a small sub-group of patients who had no symptoms preop reported them at three months (31/71 patients in PROWL-2 and 31/69 in PROWL-2). In terms of dry eye, at three months, 23 percent of patients without preoperative dry-eye symptoms developed mild dry eye, 5 percent developed moderate dry eye and 4 percent reported experiencing severe dry eye.

Dr. Manche notes, however, that a possible shortcoming in the study is that these patients were only followed for three months, and that a longer follow-up, and the potential use of enhancement procedures, would improve the results. "I've done many studies looking at LASIK outcomes and I've found that the incidence of the signs and symptoms of dry eye are most pronounced between one to three months, and then improve markedly at six to 12 months," he says. "This also applies to glare, halo and starbursts. These symptoms are more pronounced in the early postop period and then tend to subside at six to 12 months. Plus, if you look at the whole study group rather than these small subgroups, the prevalence of visual symptoms did not increase. As

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a matter of fact, the incidence of every single one of them went down. Interestingly, the Navy's PROWL-1 study reported that there were more patients with resolution of the visual symptoms that they had preoperatively than patients who developed new ones.

"Another thing that needs to be taken into account is that no enhancements were done," Dr. Manche adds. "One of the most common causes of glare and halo is residual refractive error, so it's quite possible that if you enhanced patients who also happened to complain of halo and glare that most of them would improve."

To view the study results, visit http://tinyurl.com/olqxout.

LASIK vs. the Alternatives

Indianapolis surgeon Francis Price Jr., and his wife Marianne Price, PhD, decided to conduct a prospective, multicenter, longitudinal survey study of LASIK patient satisfaction, but wanted to do it differently than it's been done in the past by including a control group. To accomplish this, they introduced a group consisting of contact lens wearers.

The initial online surveys of 2,000 patients were conducted at 22 U.S. practices and three international sites, and patients are going to be followed for three years. Fifty-nine percent of the patients underwent LASIK and the remainder continued wearing their contact lenses.

Dr. Frank Price says a control group helps researchers avoid assigning blame erroneously. "If you're going to look at patients' subjective opinions about how their vision is and how they function, you really need a control group," he says. "This is because there's a tendency to assume that any patient-reported problems after a procedure were caused by the procedure."

In terms of overall satisfaction, 98 percent of the LASIK patients and 97 percent of the contact lens patients "agree" or "strongly agree" that they'd recommend their vision correction method to a friend or family member. *(See graph, above)* Interestingly, and highlighting the usefulness of a control group, only 40 percent of the glasses and contact lens wearers reported no difficulty with night driving, and just around 10 percent reported moderate difficulty. These proportions didn't change significantly at one and two years in patients who continued in contact lenses. In the patients who had LASIK, however, the proportion who said they had no difficulty driving at night due to vision difficulties actually improved postoperatively to 60 percent. This result was maintained at two years.

On the dry-eye front, at one year 30 percent of the contact lens group reported not having any dry-eye symptoms in the past week, and 15 percent said they had some symptoms at least half the time. These results stayed relatively stable through two years.

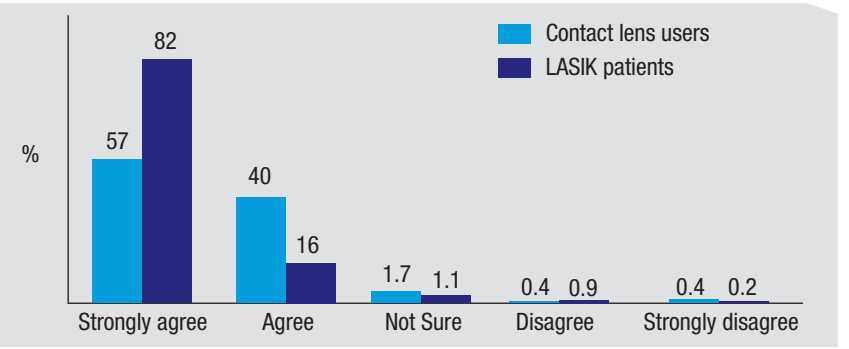
In the LASIK group, the percentage reporting never having feelings of dry eye (45 percent in both the LASIK group who had worn contacts previously and the LASIK group who had worn glasses previously) decreased at the first-year mark (down to 40 percent in contacts-to-LASIK; 26 percent in glasses-to-LASIK). This result began to improve at two years, with 46 percent of the contacts-to-LASIK group reporting no dry-eye problems and 38 percent in the glasses-to-LASIK group having no difficulties.

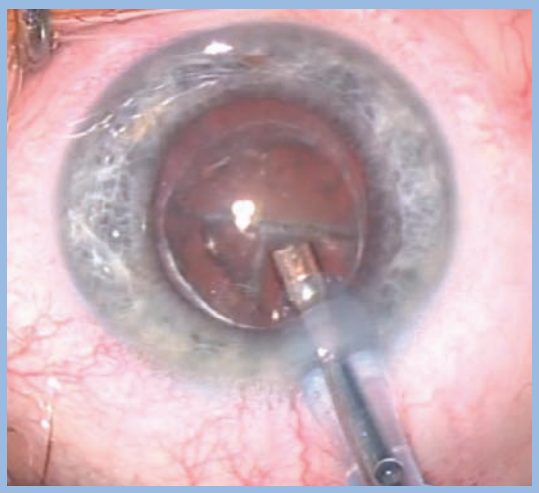
"In the patients who had worn glasses before their LASIK, there was a noticeable increase in the prevalence of dry eyes at one year," says Dr. Marianne Price. "We suspect a lot of the glasses wearers are contact lens intolerant. On the survey, we asked them if they had ever tried contact lenses, and if so, why they discontinued them, and it turned out that 75 percent had tried them, and the most common reason for discontinuing them was discomfort or dry eyes."

Dr. Frank Price says the study helped show that neither patients, nor the vision correction options they choose, are perfect. "A huge surprise was the amount of difficulty glasses wearers were having with night driving due to their vision," he says. "This was a huge surprise, especially in light of how regulatory agencies view eye-surgery studies. They tend to assume that when you wear glasses, everything is perfect. But that's not real life." REVIEW

The Prices note that their research receives no corporate funding, so any tax-deductible donations to their organization, The Cornea Research Foundation, will help them complete the three-year study.

Patients Who'd Recommend Their Form of Vision Correction





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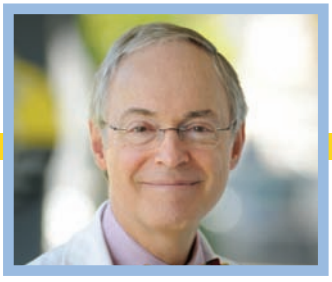

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Safety and Efficacy of Ozurdex in DME

Dexamethasone intravitreal implants (0.7 mg and 0.35 mg) met the primary endpoint for improvement in best-corrected visual acuity in two randomized, multicenter, masked and sham-controlled clinical trials in patients with diabetic macular edema. Additionally, the safety profile was acceptable and consistent with previous reports.

Patients (n=1,048) with DME, a BCVA of 20/50 to 20/200 Snellen equivalent and central retinal thickness of ≥300 µm by optical coherence tomography were randomized into a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg or sham procedure and followed for three years (or 39 months for patients treated at month 36) at ≤40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every six months. The predefined primary efficacy endpoint for the U.S. Food and Drug Administration was achievement of ≥15-letter improvement in BCVA from baseline at study end. Safety measures include adverse events and intraocular pressure.

Mean number of treatments received over three years was 4.1, 4.4 and 3.3 with DEX implant 0.7 mg, DEX implant 0.35 mg and sham, respectively. The percentage of patients with ≥15-letter improvement was greater with DEX implant 0.7 mg (22.2 percent) and DEX implant 0.35 mg (18.4 percent) than sham (12 percent; $p \leq 0.018$). Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (-111.6 µm) and DEX implant 0.35 mg (-107.9 µm) than sham (-41.9 µm; $p<0.001$). Rates of cataract-related adverse events in phakic eyes were 67.9 percent in the DEX implant 0.7-mg group; 64.1 percent in the DEX implant 0.35-mg group; and 20.4 percent in the sham group. Increases in IOP were usually controlled with medication or no therapy; only two patients (0.6 percent) in the DEX implant 0.7-mg group and one patient (0.3 percent) in the DEX implant 0.35-mg group required trabeculectomy.

Ophthalmology 2014;121:1904-1914.

This is an open access article.

Boyer D, Yoo Y, Belfort R, Bandello F, et al.

Topical NSAIDs Beneficial After Routine Cataract Surgery

Researchers in Denmark conducting a systematic literature review found high-quality evidence that topical non-steroidal anti-inflammatory drugs are more effective than topical steroids in preventing pseudophakic cystoid macular edema. The researchers also found low to moderate quality evidence that topical NSAIDs are more effective than steroids in controlling postoperative inflammation after cataract surgery.

The researchers conducted a literature search in Medline, CINAHL, Cochrane and EMBASE databases to identify randomized trials published from 1996 onward comparing steroids with topical NSAIDs in controlling inflammation and preventing PCME in patients undergoing phacoemulsification with posterior chamber intraocular lens implantation for age-related cataract. Fifteen randomized trials were identified. Postoperative inflammation was less in patients randomized to NSAIDs. The prevalence of PCME was significantly higher in the steroid group than in the NSAID group: 3.8 percent vs. 25.3 percent of patients (r: 5.35; 95 percent confidence interval, 2.94 to 9.76).

Ophthalmology 2014;121:1915-1924.

Kessel L, Tendal B, Jørgensen K, Erngaard D, et al.

A Novel Drug Coating for Glaucoma Drainage Devices

Researchers from Tulane have developed a novel, porous coating for Ahmed glaucoma valves based on biodegradable poly(lactic-co-glycolic acid), which allows for the combined use of both mitomycin-C and 5-fluorouracil to inhibit cell proliferation in a tissue culture model. This has the potential to reduce fibrosis and

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increase the success rate for glaucoma drainage devices.

Thin films of PLGA were fabricated using a spin-coating technique. The procedure led to an asymmetric pore structure that was exploited to control the rate of dissolution. Double-layered porous films were constructed to achieve continuous drug release, providing a burst release of mitomycin-C followed by a slow release of 5-FU, which together prevented fibrosis over the most active period of postoperative wound healing (zero to 28 days). Double-layered films containing only 5-FU in the bottom layer showed a three to five day delay in drug release, followed by a sharp increase that continued for 28 days. Mitomycin-C was only stable when it was surface-loaded; it was therefore surface-loaded onto the top PLGA layer to provide a continuous release of antifibrotics over the wound-healing period.

J Glaucoma 2014;23:526-534.
Ponnusamy T, Yu H, Jon V, Ayyala R, et al.

Safety and Efficacy of PRK: 20-year Follow-up

Researchers from the Keratoconus Research Institute in London found, in a 20-year observational study investigating the safety and efficacy of photorefractive keratectomy, that there was a slight but significant increase in myopic spherical equivalent refractive error after PRK between one and 20 years, particularly in those under 40 at the time of treatment and in female patients. Corneal power remained unchanged but axial length increased. Overall, the procedure was safe, with no long-term, sight-threatening complications and with improvements in corrected distance visual acuity and corneal transparency with time.

In the setting of a university hospital, a study population of 42 patients (42 eyes) who had, as part of a randomized, prospective trial, undergone PRK 20 years previously were studied. All had received either -3 D or -6 D corrections with either 5 or 6 mm optical zones or a multizone treatment. The mean preoperative SEQ was -5.13 D (r: -2.75 to -8 D). The outcome measures included visual acuity, refractive error, corneal topography and axial length.

Between one and 20 years there was an increase in mean myopic SEQ of -0.54 D ($p<0.02$). In patients younger than 40 years of age at the time of correction, this increase was -0.92 D ($p<0.002$) with an accompanying increase in variance ($p<0.02$), whereas in those older than 40 it was -0.08 D ($p=0.8$). In female patients the change was -0.69 D ($p<0.01$), while in males it was -0.26 D ($p=0.6$). The efficacy index at 20 years was 0.49 and the safety index was 0.97. Corrected distance visual acuity improved between one and 20 years ($p<0.01$); 93 percent of corneas were clear at 20 years; three eyes had trace haze. There was an improvement in haze scores between one and 20 years ($p<0.02$). Cornea power remained unchanged between six months and 20 years ($p=0.4$). Axial length increased by a mean of 0.84 ($p<0.0001$), and there was no ectasia.

Am J Ophthalmol 2014;158:651-663.
O'Brart D, Shalchi Z, McDonald R, Patel P, et al.

Evaluating Presbyopia-Correcting IOLs After Bilateral Implants

In a clinical trial comparing contrast sensitivity, visual acuity and halos in subjects bilaterally implanted with one of three FDA-approved presbyopia-correcting intraocular lenses, the Crystalens AO (Bausch + Lomb Surgical) had statistically better uncorrected intermediate visual acuity and distance-corrected intermediate visual acuity than the AcrySof IQ ReSTOR +3.0 (Alcon Laboratories) or Tecnis Multifocal (Abbott Medical Optics) lenses. The Crystalens AO also had fewer photic phenomenon than the Tecnis Multifocal lens. However, both the ReSTOR +3.0 and the Tecnis Multifocal lenses had better distance-corrected near visual acuity and uncorrected near visual acuity than the Crystalens AO.

Subjects (n=78) were randomized sequentially in a partially masked, multicenter trial for bilateral implantation with the Crystalens AO, ReSTOR +3.0 or Tecnis Multifocal lenses. Subjects were evaluated through visit four (four to six months after surgery) with the following monocular and binocular assessments: high- and low-contrast visual acuity; contrast sensitivity without glare, halos or starbursts; defocus curves; optical scatter; retinal point spread function; and safety.

The Crystalens AO and ReSTOR +3.0 demonstrated better monocular and binocular contrast sensitivity without glare at low to mid spatial frequencies compared with the Tecnis Multifocal lens. Binocular uncorrected distance visual acuity was not significantly different between the lenses. The Crystalens AO had significantly better binocular low-contrast distance-corrected visual acuity than the ReSTOR +3.0 and better mean monocular low-contrast DCVA than the Tecnis Multifocal lens. The Crystalens AO demonstrated significantly better monocular and binocular uncorrected and distance-corrected intermediate visual acuity than the ReSTOR +3.0 or Tecnis Multifocal lens. The ReSTOR +3.0 lens had significantly better monocular and binocular uncorrected and distance-corrected near visual acuity tested at 40 cm compared with the Crystalens AO and the Tecnis Multifocal lens. The Crystalens AO elicited significantly less occurrence of halos than the Tecnis Multifocal lens and less optical scatter than either the ReSTOR +3.0 or Tecnis Multifocal lens.

Am J Ophthalmol 2014;158:436-446.
Pepose J, Qazi M, Chu R, Stahl J.

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The recent return of earlier floaters and decreased vision in one eye mark the latest signs in a patient with previous vitreous detachment.

Nathan Cutler, MD

Presentation

A 59-year-old Caucasian woman presented with a one-month history of increased floaters and decreased vision in her left eye. She stated that her vision was previously equal in both eyes. She was initially evaluated for the floaters four months prior to presentation and found to have a posterior vitreous detachment without evidence of retinal tears or detachments at that time. She denied any history of trauma, pain, headache or neurologic symptoms.

Medical History

The patient's past ocular history was only significant for the aforementioned posterior vitreous detachment. Her past medical history was significant for multiple myeloma; squamous cell carcinoma (nose); basal cell carcinoma (neck); herpes zoster; hypertension; gastroesophageal reflux disease; and anxiety. Her medications included filgrastim (G-CSF); plerixafor (immunostimulant); acyclovir; gabapentin; lidocaine; metoprolol; nifedipine; omeprazole; lorazepam; and calcitriol. Allergies included erythromycin. Her family history was significant for breast, lung and colon cancer, diabetes mellitus and rheumatoid arthritis. The patient was a former smoker, but stopped 22 years ago. Social history was negative for alcohol or drug use.

With regard to her history of multiple myeloma, she was first diagnosed six months prior to presentation and had completed five months of chemotherapy. She had since been in remission and was in the process of preparing for stem cell collection and autologous implantation.

Examination

The patient's vital signs were stable and within normal limits. Her visual acuity was 20/30 with improvement to 20/25 pinhole in the right eye and 20/60 in the left eye without improvement on pinhole. External examination showed moderate ptosis in both eyes with the right slightly greater than the left. There was no proptosis in either eye. Pupils were equal and reactive without afferent pupillary defect. Confrontational visual fields were full to finger counting in both eyes. Extraocular motility was full in both eyes. Intraocular pressure was 13 mmHg in the right eye and 15 mmHg in the left eye.

Figure 1. Fundus photographs of the right eye (left) and left eye (right) on presentation. The left eye shows vitreous haze, retinitis and a chorioretinal scar.

Anterior slit-lamp examination of the right eye was normal. The left eye showed multiple keratic precipitates and 2+ cell and flare present in the anterior chamber. Funduscopic examination of the right eye was normal. Funduscopic examination of the left eye showed significant vitreous haze, mildly attenuated vessels along with perivascular cuffing along the veins, and an intraretinal lesion measuring 6 x 6 mm approximately 5 mm superiotemporal to the nerve *(See Figure 1)*. An old 2 x 1 mm chorioretinal scar was also present.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 64

Diagnosis, Workup and Treatment

With our patient's medical history of multiple myeloma and SCC, the finding of a retinal lesion was concerning for possible neoplastic etiologies including plasmacytoma, metastatic SCC or lymphoma. Plasmacytomas can be found as solitary tumors or in association with multiple myeloma as either a first manifestation of systemic disease or insufficient treatment. They can rarely present in the eye and have appeared in the eyelid, conjunctiva and orbit and as uveal lesions affecting the iris, ciliary body or choroid.[1-3] However, the presence of anterior and posterior inflammation focused our differential on more infectious processes including toxoplasmosis, syphilis, tuberculosis, toxocariasis, cytomegalovirus or candidiasis. Acute retinal necrosis (ARN) was also high on the differential. While ARN is more typically seen with VZV, it can also be caused by HSV, EBV or CMV.[4] Additionally, breakthrough ARN can occur despite prophylactic use of acyclovir, which our patient was taking.[5] Inflammatory lesions including sarcoid, lupus and Wegener's were also considered.

A B-scan revealed cells in the vitreous as well as choroidal thickening. Optical coherence tomography demonstrated hyperreflective lesions on the retinal surface consistent with inflammatory precipitates along with choroidal thickening *(See Figure 2)*.

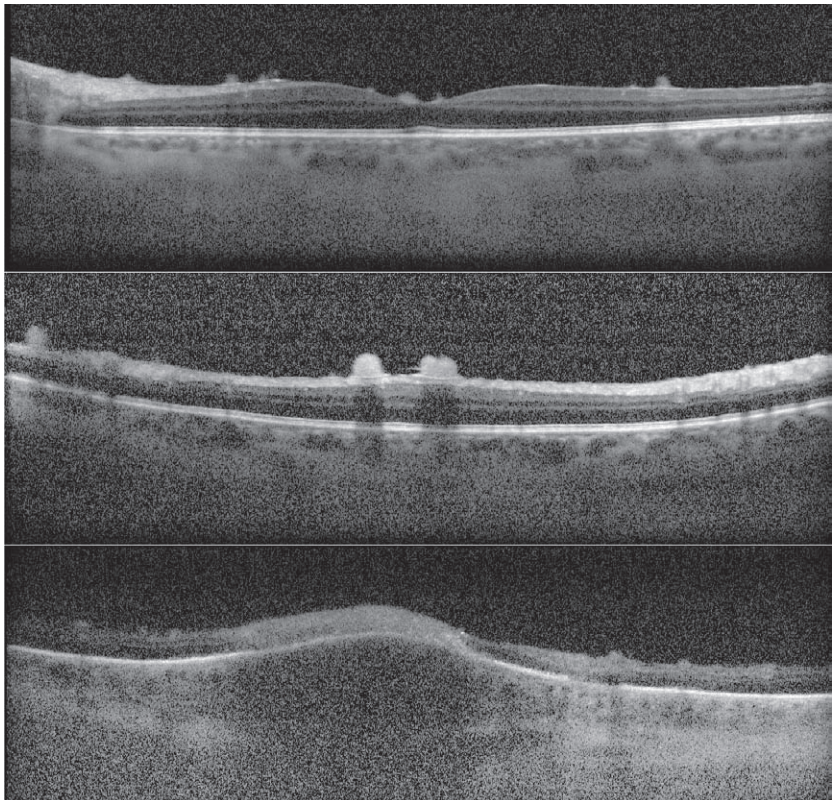

Figure 2. OCT of the right eye through the macula (top), the parafoveal retina (middle) and the retinal lesion (bottom) on presentation. Inflammatory precipitates are present on top of the retinal surface, while the lesion shows choroidal thickening.

Laboratory studies on presentation were significant for a white blood cell count of 64,600 per mm3 with 45 percent monocytes and only 5 percent segmented neutrophils. This unusual blood count was consistent with her current use of plerixafor, an immunostimulant that mobilizes hematopoietic stem cells and is used prior to autologous transplant in cancer patients. This clinical picture and diagnostic results were consistent with a diagnosis of ocular toxoplasmosis. The patient was treated with trimethoprim/sulfamethoxazole for six weeks and her vision slowly improved. By seven weeks, all of the inflammation in her left eye had resolved and her vision in the left eye had improved to 20/40.

Discussion

Ocular toxoplasmosis, a disease caused by the parasite *Toxoplasma gondii*, accounts for 25 percent of posterior uveitis cases in the United States today. While cats are the definitive hosts, humans serve as intermediate hosts to *T. gondii* and approximately one-third of the human population worldwide is infected by the parasite. Ocular manifestations are generally found in only 2 percent of those infected.[6,7]

While it was traditionally thought that the majority of human infection by *T. gondii* occurred most commonly by congenital transplacental transmission, it is now known that acquired infections are the most common causes of ocular toxoplasmosis and ocular lesions may first develop years after initial infection.[7] Acquired transmission can occur through ingestion of undercooked, infected meat; contaminated water, fruit or vegetables; unpasteurized goat milk from a chronically infected animal; or contact with cat feces or cat litter.

Patients with ocular toxoplasmosis often describe blurred or hazy vision and floaters with absence of pain. Up to 20 percent of patients have acute ocular hypertension at presentation.[8] On fundus exam, most commonly there will be unilateral bright white-yellow retinal lesions, which are often associated with an old pigmented chorioretinal scar.[8] Retinal hemorrhages are usually absent. Universally, there is significant vitritis, resulting in the classic "headlight in fog" appearance on indirect ophthalmoscopy. Perivasculitis with diffuse venous sheathing can be seen as well. Anterior chamber spillover can occur, and there can be associated scleritis or neuroretinitis. Rarely, immunosuppressed patients can present with a more diffuse, progressive retinitis not associated with an adjacent chorioretinal scar.

The diagnosis is most often made clinically, based on characteristic fundus lesions. In patients with atypical presentations or in whom there is inadequate response to initial therapy, anterior chamber or vitreous PCR or diagnostic vitrectomy can be useful tools to rule out toxoplasmosis infection.[9] IgM antibodies will rise early after infection and remain detectable for less than one year while IgG antibodies will appear within the first two weeks after infection and remain detectable for life. Because these antibodies are highly sensitive markers of the disease state, antibody testing is helpful in ruling out toxoplasmosis when the result is negative.

When treating ocular toxoplasmosis, the goal is to stop parasitic replication and reduce intraocular damage due to the associated inflammatory response. The infection is most often self-limited in immunocompetent patients and small extramacular lesions can be observed untreated with resolution to pigmented scars over the course of one to two months. However, in immunocompromised patients, the disease can be much more severe and progressive. Antibiotic treatment should be offered for sight-threatening lesions, such as those with zone 1 or zone 2 involvement, infants up to 1 year old, patients with severe inflammation or in patients with persistent symptoms or significant loss of vision.

Traditional therapy consists of 75 to 100 mg of pyrimethamine daily for two days followed by a 25- to 50-mg daily dose and 2 to 4 g of sulfadiazine daily for two days followed by a 0.5- to 1-g dose four times a day.[10] Folinic acid is also used at 5 mg daily three times a week during pyrimethamine therapy to protect against leukopenia and thrombocytopenia. Concomitant prednisone therapy of 0.5 to 1 mg/kg daily is also often used to reduce inflammation, however this should not be used without antibiotics or in the immunocompromised patient. Trimethoprim/sulfamethoxazole 160/800 mg twice daily has been shown to be equivalent to the traditional triple-therapy regimen.[10] Other oral treatment regimens have been used including azithromycin, clindamycin and atovaquone alone or combined with the aforementioned treatments. Intravitreal clindamycin plus dexamethasone is perhaps safer and more convenient than conventional oral therapy and has also been shown to be equally as effective.[11] There is little evidence to support one antibiotic regimen over another, and treatment regimens should be based on the clinical presentation and safety profile of the intended treatment.[12]

Patients who are immunocompromised, especially those with HIV/AIDS, should have brain imaging performed, as there is a high frequency of cerebral involvement associated with ocular disease. These patients also often need long-term antitoxoplasmic medication, as they are at greater risk of disease recurrence. A prospective, randomized clinical trial conducted in Brazil, where the incidence of toxoplasmosis infection is as high as 85 percent, demonstrated that maintenance trimethoprim/sulfamethoxazole therapy reduced the incidence of recurrent toxoplasmosis retinochoroiditis from 13 percent on placebo to 0 percent on treatment over a one-year period.[13]

Ocular toxoplasmosis is a common cause of posterior uveitis worldwide. A bright yellow or gray-white retinal lesion through dense vitritis with adjacent pigmented scar is considered pathognomonic for the diagnosis. While most cases are self-limited, better-tolerated and possibly safer treatment options such as trimethoprim/sulfamethoxazole or intravitreal clindamycin offer the ophthalmologist greater flexibility in tailoring treatment to each patient. REVIEW

The author thanks Marc Spirn, MD, of the Wills Retina Service for his time and assistance in preparing this report.

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RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATION AND USAGE

RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

ADVERSE REACTIONS

Clinical Trials Experience

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

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Post-marketing Experience

The following adverse reactions have been identified during post approval use of **RESTASIS®** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Rx Only

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RESTASIS® twice a day, every day, helps patients experience increased tear production

Increased tear production was seen at 6 months.[1]

Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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

Reference: 1. RESTASIS® Prescribing Information.

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