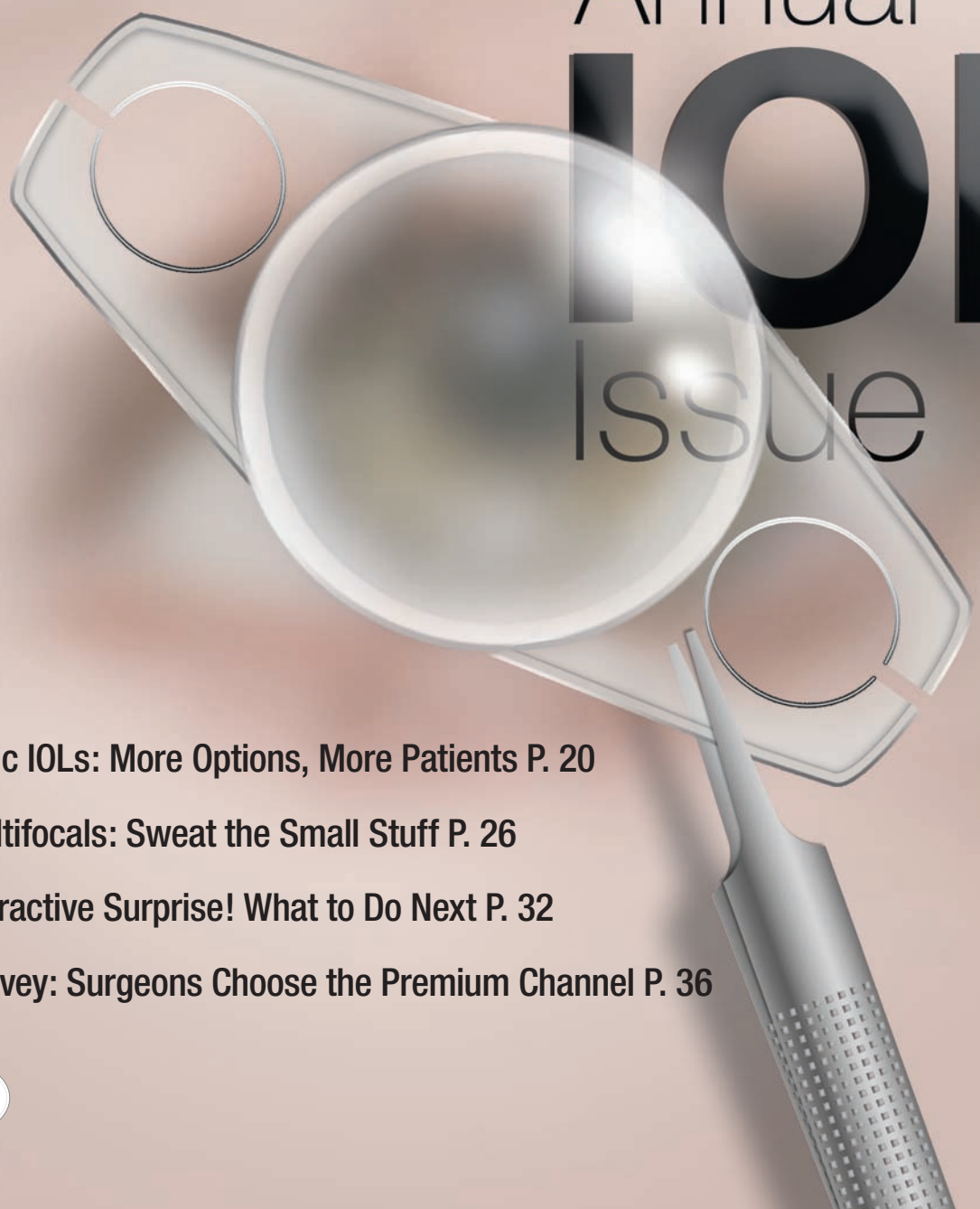
REVIEW® of Ophthalmology

January 2014 • revophth.com

Annual IOL Issue



jmi

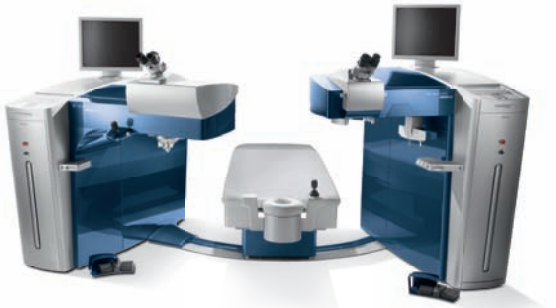
The Integrated WaveLight® Refractive Suite

The world's fastest refractive platform features:

- Unrivaled 500 Hz Excimer Laser ablation times at just **1.4 seconds per diopter***
- Precise 200 kHz Femtosecond Laser custom flap creation in **6 seconds***
- A 1050 Hz-type Eye Tracker, synchronized at 500 Hz, with **2 millisecond latency time**
- A broad range of customized, patient-specific treatments available

Ask your Alcon Sales Representative for more information.

*Based on typical treatment parameters for myopia.
For important safety information about this product, please refer to the adjacent page.



WaveLight® FS200
Femtosecond Laser

WaveLight® EX500
Excimer Laser

Alcon®
a Novartis company

WaveLight®
Refractive Suite

WaveLight®

Important Safety Information about the WaveLight® Excimer Laser Systems

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q , and the WaveLight® EX500.

Caution: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System.

Indications: FDA has approved the WaveLight® Excimer Laser for use in laser-assisted in situ keratomileusis (LASIK) treatments for:

- the reduction or elimination of myopia of up to - 12.0 DS and up to 6.0 D of astigmatism at the spectacle plane;
- the reduction or elimination of hyperopia up to + 6.0 DS with and without astigmatic refractive errors up to 5.0 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.0 D;
- the reduction or elimination of naturally occurring mixed astigmatism of up to 6.0 D at the spectacle plane; and
- the wavefront-guided reduction or elimination of myopia of up to -7.0 DS and up to 3.0 D of astigmatism at the spectacle plane.

The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia.

Contraindications: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who:

- are pregnant or nursing;
- have a diagnosed collagen vascular, autoimmune or immunodeficiency disease;
- have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; or
- are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*).

Warnings: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have:

- systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status;
- a history of Herpes simplex or Herpes zoster keratitis;
- significant dry eye that is unresponsive to treatment;
- severe allergies; or
- an unreliable preoperative wavefront examination that precludes wavefront-guided treatment.

The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment.

Precautions: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with:

- progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone;
- corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage;
- residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia;
- pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning;
- history of glaucoma or ocular hypertension of > 23 mmHg;
- taking the medication sumatriptan succinate (Imitrex*);
- corneal, lens and/or vitreous opacities including, but not limited to cataract;
- iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or
- taking medications likely to affect wound healing including (but not limited to) antimetabolites.

In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for:

- treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or
- wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted;

In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population.

Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery.

Adverse Events and Complications

Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination.

The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect.

Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination.

The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface.

Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees.

The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye.

Wavefront-Guided Myopia: No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort (traditional LASIK treatment) one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye.

The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort.

Clinical Data

Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline).

Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months.

Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%).

Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months.

Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline).

Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months.

Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%.

Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20.

In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline).

Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months.

Information for Patients: Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries.

Attention: Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

* Trademarks are property of their respective owners.

Alcon®

a Novartis company

REVIEW NEWS
Volume XXI • No. 1 • January 2014

Hope for Cataract Prevention Gets Boost from UCI Research

Groundbreaking new findings by University of California, Irvine and German chemists about how cataracts form could be used to help prevent the world's leading cause of blindness, which currently affects nearly 20 million people worldwide.

"That's the dream, and this is a big step," said Rachel Martin, PhD, UC Irvine associate professor of chemistry and co-author of a paper featured in the December issue of the journal *Structure*. "Understanding the molecular mechanism of what goes wrong in the eye that leads to a cataract could lead to the development of better treatment options, including more sophisticated artificial lenses and drugs."

It has long been known that human eyes have a powerful ability to focus because of three kinds of crystallin proteins in their lenses, maintaining transparency via a delicate balance of both repelling and attracting light. Two types of crystallin are structural, but the third—dubbed a "chaperone"—keeps the others from clumping into cataracts if they're modified by genetic mutation, ultraviolet light or chemical damage.

The UC Irvine team painstakingly explored and identified the structures of the normal proteins and a genetic mutation known to cause cataracts in young children. They found that the chaperone proteins bind far more strongly to the mutated proteins in an effort to keep the lens clear. One major problem: Every human eye contains a finite number of the helpful proteins. Once they're used up, the researchers learned, weakened ones quickly begin to aggregate and form blinding cataracts.

Now that this mechanism has been mapped at the molecular level, the team is hopeful that organic chemists can create sight-saving treatments to prevent such aggregation.

While people with adequate medical care can have corrective surgery for cataracts, the World Health Organization has found that millions suffer major vision loss because they do not have access to laser surgery or other options. By 2019, the number of people older than 50 with impaired sight is expected to grow even higher, particularly in China, India, Southeast Asia and Eastern Mediterranean nations.

Novel Removal Method May Mean Stem Cell Advance

Researchers in the Cedars-Sinai Regenerative Medicine Institute have designed and tested a novel, minute-long procedure to prepare human amniotic membrane for use as a scaffold for specialized stem cells that may be used to treat some corneal diseases. This membrane serves as a foundation that supports the growth of stem cells in order to graft them onto the cornea.

This new method, explained in a paper published this month in the journal *PLoS ONE*, may accelerate research and clinical applications for stem cell corneal transplantation.

Corneal blindness affects more than 8 million people worldwide. Among other causes, corneal blindness can be the outcome of corneal stem cell deficiency, a disease usually resulting from genetic defects or injury to the eye—such as burns, infection or chronic inflammation—that can lead to vision loss. A feasible treatment to rectify vision loss for such patients is corneal stem cell transplantation, either as a biopsy from another eye or by transplanting cultured stem cells, although this promising approach is not yet fully standardized.

An approved biological foundation for cultured stem cells is the human amniotic membrane. For the best growth of stem cells, amniotic cells need to be removed by chemical agents. The existing methods for removing these cells from this membrane are not standardized, leave behind amniotic cells and may cause unwanted loss of some of the membrane components.

The amniotic cell removal method created at Cedars-Sinai takes less than one minute and ensures virtually complete amniotic cell removal and preservation of amniotic membrane components, and also supports the overall growth of various stem and tissue cells.

"We believe that this straightforward and relatively fast procedure would allow easier standardization of amniotic membrane as a valuable stem cell support and improve the current standard of care in corneal stem cell transplantation," said lead author Alexander Ljubimov, PhD, director of the Eye Pro-

Correction

In the November 2013 article, "Cracking the Code of ICD-10," the ICD-10 code given for primary open-angle glaucoma is incorrect. The correct code is H40.11x, followed by a seventh digit for describing the severity.

gram at the Cedars-Sinai Regenerative Medicine Institute. "This new method may provide a better method for researchers, transplant corneal surgeons and manufacturing companies alike."

Mehrnoosh Saghizadeh Ghiam, PhD, a research scientist in the Regenerative Medicine Institute's Eye Program, assistant professor in the department of Biomedical Sciences and first author of the study, commented on the potential of the new method.

"The amniotic membrane has many beneficial properties and provides an attractive framework to grow tissue and stem cells for regenerative medicine transplantations, especially in replacing missing stem cells in the cornea," said Dr. Saghizadeh. "Our method for preparing this scaffold for cell expansion may streamline clinical applications of cell therapies."

Study: RD/ Drug Link Unfounded

In contrast to findings of a recent study, researchers in Denmark did not find an association between use of a class of antibiotics known as fluoroquinolones (such as ciprofloxacin) and an increased risk of retinal detachment, according to a study appearing in the November 27 issue of *JAMA*.

A recent study found that use of fluoroquinolones was strongly associated with retinal detachment, reporting a 4.5-fold significantly increased

risk for ongoing exposure. A possible mechanism was effects of the drug on connective tissue, according to background information in the article: "Given the prevalent use of fluoroquinolones, this could, if confirmed in the general population, translate to many excess cases of retinal detachment that are potentially preventable."

Bjorn Pasternak, MD, PhD, of the Statens Serum Institut, Copenhagen, and colleagues used data from a nationwide register to investigate whether oral fluoroquinolone use was associated with increased risk of retinal detachment. The register had information about 748,792 episodes of fluoroquinolone use and 5,520,446 control episodes of nonuse, including data on participant characteristics, drugs used and cases of retinal detachment with surgical treatment.

The fluoroquinolones used were ciprofloxacin (88.2 percent), ofloxacin (9.2 percent), fleroxacine (1.2 percent), moxifloxacin (0.8 percent) and others (0.7 percent).

Of 566 patients with retinal detachment, 72 were exposed to fluoroquinolones; five during current use (days one to 10), 7 during recent use (days 11 to 30), 14 during past use (days 31 to 60) and 46 during distant use (two to six months). Among patients not exposed to fluoroquinolones, 494 cases occurred. Analysis of the data indicated that fluoroquinolone use compared with nonuse was not associated with increased risk of retinal detachment.

The authors write that given limited power, the study can only rule out more than a threefold relative increase in the risk of RD associated with current fluoroquinolone use. However, any differences in absolute risk are likely to have limited, if any, clinical significance: In terms of absolute risk, current use of fluoroquinolones would, in the worst-case scenario, account for no more than 11 additional cases of retinal detachment per 1,000,000 treatment episodes. REVIEW

All Pupil II

Vantage Plus

Spectra Iris

Vantage Plus
Digital

Get a
Free Keeler Indirect
When You
Buy Any 3 Keeler Indirects,
& Trade-In Any 3 Indirects
through March 31, 2014

Learn more at www.keelerusa.com

For years, we've been telling you that Keeler* is the world leader in innovation, technology, and market share.

- *First Wireless Indirect*
- *First LED indirect*
- *First Digital Indirect*
- *First Intelligent Optical System*
- *Patented Hi-Mag Lens*

Buy Online!
keelerusa.com

Keeler
OPTICS

*iData Research Inc. 2011 – "Keeler Instruments was the leading competitor in the U.S. market for BIOs with a share of 63.6%.". "The binocular indirect ophthalmoscope market has seen a great deal of innovation over the years. Keeler Instruments has been at the forefront of this innovation".

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

REVIEW Editorial Board

Contributors

Advisory Board

Jobson Professional Publications Group

BUSINESS OFFICES
11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
SALES MANAGER, NORTHEAST,
MID ATLANTIC, OHIO
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

SALES MANAGER, SOUTHEAST, WEST
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

VICE PRESIDENT OF OPERATIONS
CASEY FOSTER
(610) 492-1007 CFOSTER@JOBSON.COM

MANAGER EDUCATIONAL CONFERENCES/MEETINGS
MEG McDONALD
(610) 492-1045 MMCDONALD@JOBSON.COM

PRODUCTION MANAGER
SCOTT TOBIN
(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL: **RHSUBS@HALLDATA.COM**
CIRCULATION E-MAIL: **RHSUBS@HALLDATA.COM**

CIRCULATION
PO BOX 2026, SKOKIE, IL 60076
(877) 529-1746
OUTSIDE USA: (847)763-9630
FAX: (847)763-9631

SENIOR CIRCULATION MANAGER
ANTHONY GUADAGNINO
(212) 219-7870 aguadagnino@jobson.com

CHIEF OPERATING OFFICER
JEFF MACDONALD

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, HUMAN RESOURCES
LORRAINE ORLANDO

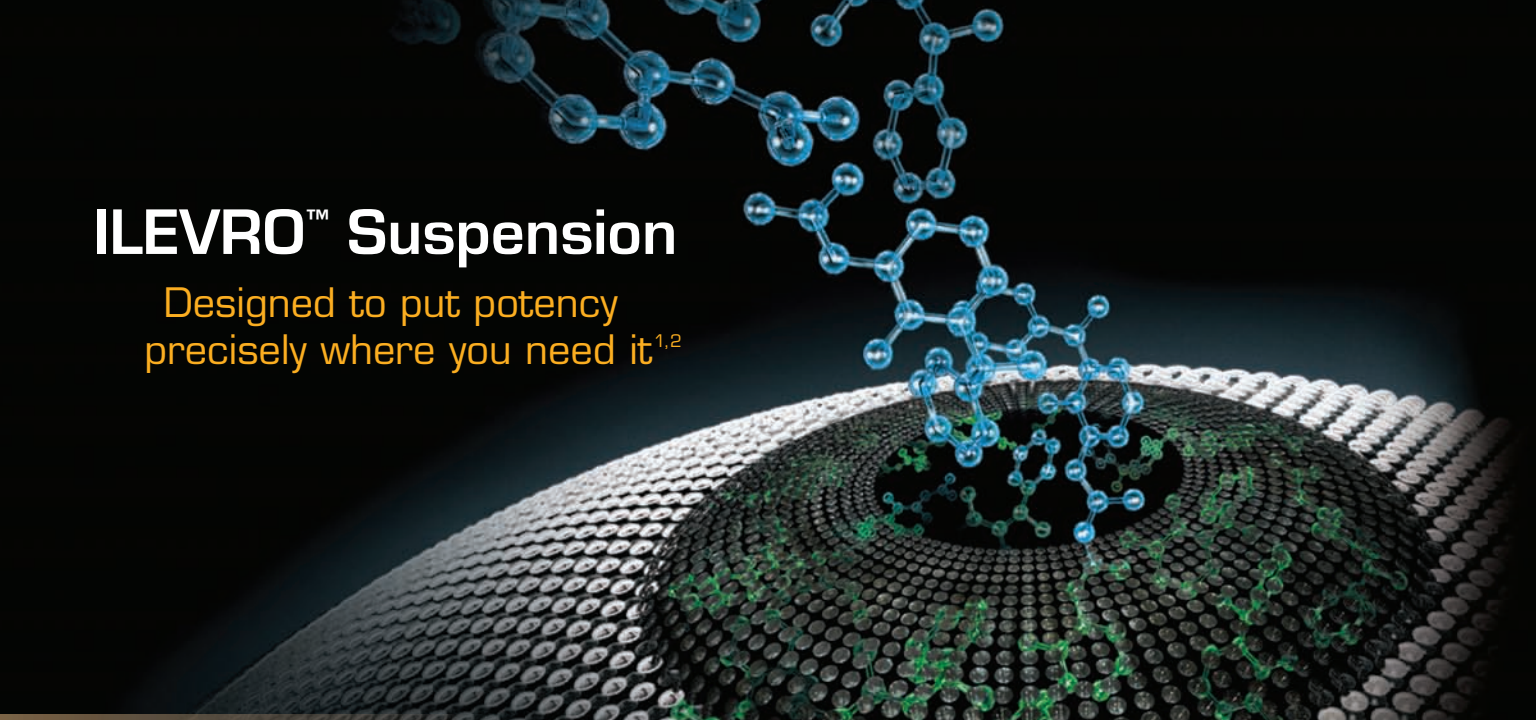
VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi

100 Avenue of the Americas
New York, NY 10013

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 100 Avenue of the Americas, New York, NY 10013-1678. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 2026, Skokie, IL 60076, USA. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (847) 763-9631. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.V



ILEVRO™ Suspension

Designed to put potency precisely where you need it[1,2]

ONCE-DAILY POST-OP

One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

Use of ILEVRO™ Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

INDICATIONS AND USAGE

ILEVRO™ Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

  Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO™ Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO™ Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

ILEVRO™ (nepafenac ophthalmic suspension) 0.3%

Alcon®

a Novartis company

 2/13 ILV13030JAD

ILEVRO™

(nepafenac ophthalmic suspension) 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO™ Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO™ Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO™ Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO™ Suspension and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO™ Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO™ Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO™ Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to 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.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

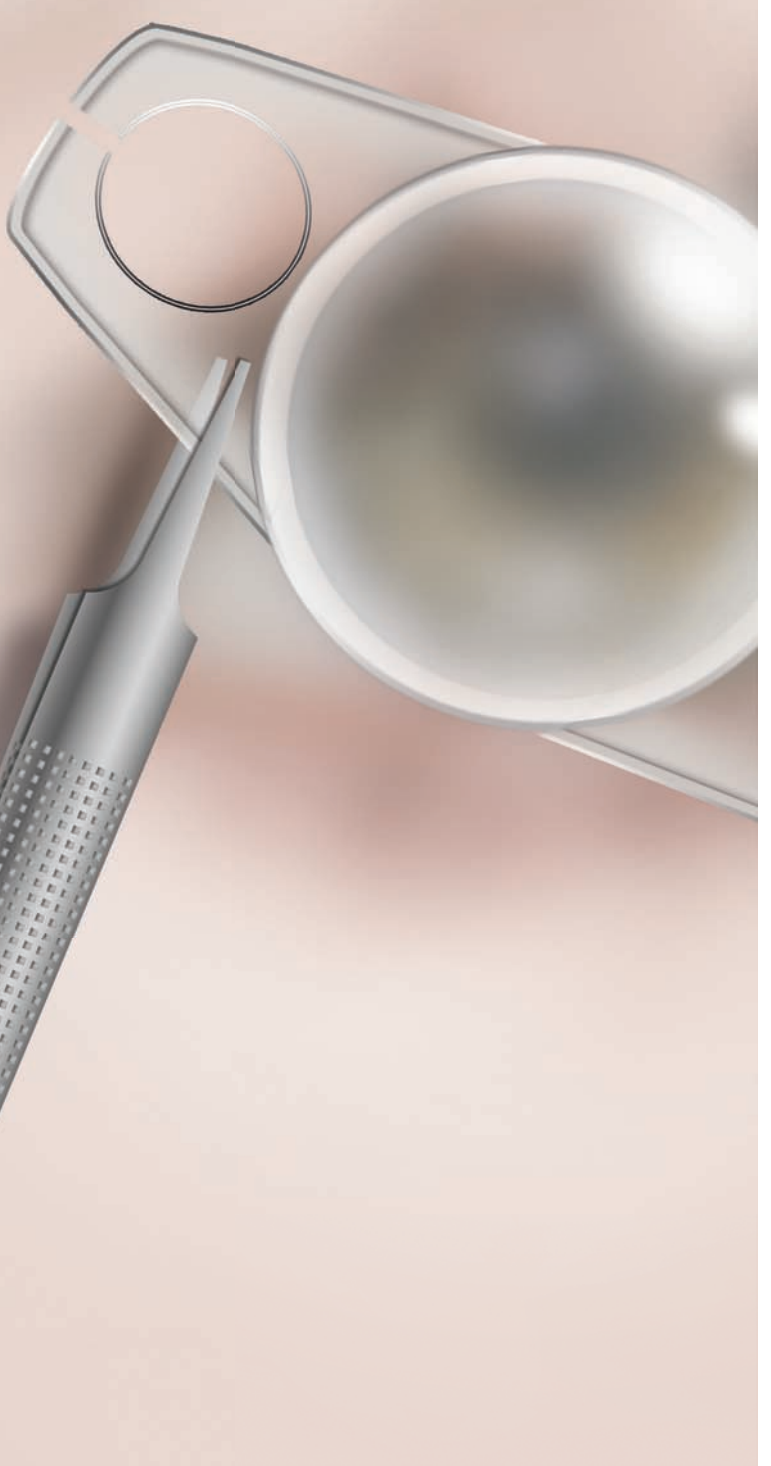
Alcon®

a Novartis company

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

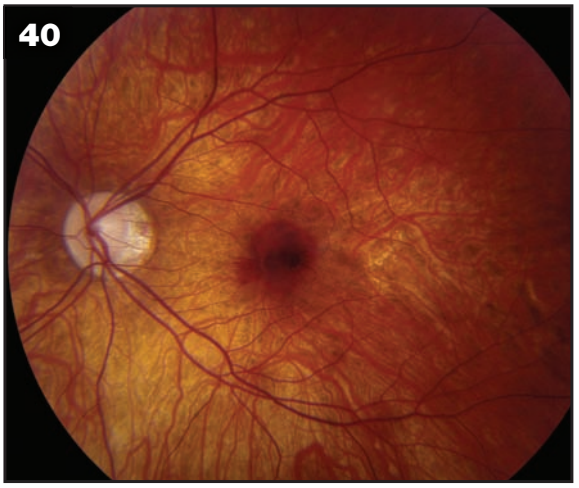
REVIEW® of Ophthalmology

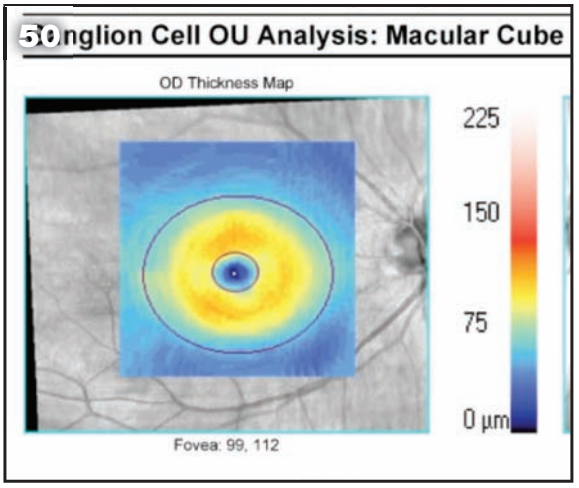
January 2014 • Volume XXI No. 1 | revophth.com

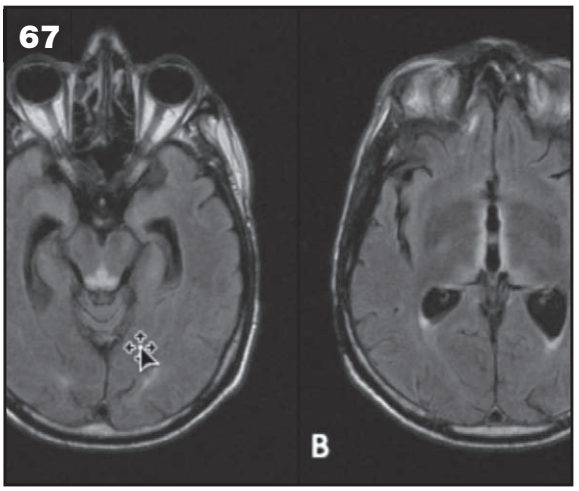


Cover Focus

Departments







Introducing the TECNIS® Toric IOL

Secure rotational stability. Deliver precise outcomes.

The **TECNIS®** Toric IOL exceeds the ANSI (American National Standards Institute) criteria for toric lens rotational stability*[1] – a critical factor in postoperative visual outcomes.[2]

The IDE study showed:

- 94% of eyes had a change of axis ≤5° between baseline and six months[1]
- Average rotation during the same time period was 2.74°[1]

Experience the proven performance of the TECNIS® Toric IOL today.
Visit www.TECNISToricIOL.com or call 1-877-AMO-4-LIFE.

Indications: The TECNIS® Toric 1-Piece posterior chamber lenses are indicated for the visual correction of aphakia and pre-existing corneal astigmatism of one diopter or greater in adult patients with or without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire improved uncorrected distance vision, reduction in residual refractive cylinder, and increased spectacle independence for distance vision. The device is intended to be placed in the capsular bag. **Warnings:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any circumstances described in the TECNIS® Toric 1-Piece IOL Directions for Use that could increase complications or impact patient outcomes. The clinical study did not show evidence of effectiveness for the treatment of preoperative corneal astigmatism of less than one diopter. The TECNIS® Toric 1-Piece IOL should not be placed in the ciliary sulcus. Rotation of the TECNIS® Toric 1-Piece IOL away from its intended axis can reduce its astigmatic correction. Misalignment greater than 30° may increase postoperative refractive cylinder. **Precautions:** Accurate keratometry and biometry in addition to the use of the TECNIS Toric Calculator (www.TECNISToricCalc.com) are recommended to achieve optimal visual outcomes. The safety and effectiveness of the toric intraocular lens have not been substantiated in patients with certain preexisting ocular conditions and intraoperative complications. Refer to the TECNIS® Toric 1-Piece IOL Directions for Use for a complete description of the preexisting conditions and intraoperative complications. All preoperative surgical parameters are important when choosing a toric lens for implantation. Variability in any of the preoperative measurements can influence patient outcomes. All corneal incisions were placed temporally in the clinical study. Do not reuse, resterilize, or autoclave. **Adverse Events:** The most frequently reported adverse event that occurred with the TECNIS® Toric 1-Piece IOL was surgical reintervention, which occurred at a rate of 3.4% (lens repositioning procedures and retinal repair procedures). Other reported events included macular edema, which occurred at a rate of 2.9% and retinal detachment, which occurred at a rate of 0.6%. **Caution:** Federal law restricts this device to sale by or on the order of a physician. **Attention:** Reference the Directions for Use labeling for a complete listing of Indications, Warnings and Precautions.

TECNIS® Toric Aspheric IOL TORIC

The newest addition to the **TECNIS®** family of IOLs. **For your peace of mind.**

*ANSI Z80.30-2010 requires that >90% of eyes experience a change in axis of ≤5° between two consecutive visits approximately three months apart.

1. TECNIS Toric 1-Piece IOL [package insert]. Santa Ana, Calif: Abbott Medical Optics Inc.
2. Novis C. Astigmatism and toric intraocular lenses. *Curr Opin Ophthalmol.* 2000; 11:47-50.

Abbott Medical Optics

Besivance®
besifloxacin ophthalmic suspension, 0.6%

By Cathleen McCabe, MD

A Good Choice for Treating Bacterial Conjunctivitis

When it comes to treating bacterial conjunctivitis, this fluoroquinolone antibiotic has proven efficacy. Find out why.

More than four million Americans suffer from bacterial conjunctivitis each year,[1] with patients most often seeking consultation for complaints of secretions and red, inflamed eyes. Patients often complain of mucous discharge with lid crusting, tearing and foreign body sensation.

Microorganisms associated with bacterial conjunctivitis include *Staphylococcus aureus*, *Streptococcus pneumonia*, *Pseudomonas aeruginosa* and *Haemophilus influenza*. From 2000 to 2005, there has been an increasing incidence of methicillin-resistant *S. aureus* (MRSA) in serious ocular infections in the United States.[2] Not surprisingly, cases of MRSA and other resistant organisms, such as methicillin-resistant *Staphylococcus epidermidis* (MRSE), have become a serious potential complication and a concern for ophthalmologists who manage ocular infections.

Although generally self-limited, bacterial conjunctivitis is frequently treated with topical antibiotics to decrease the duration of the infection and limit its spread to other patients. Several antibiotic classes are available, but fluoroquinolones are considered by many to be an antibiotic of choice because of their dosing regimen, broad-spectrum coverage and safety profile. Here, we'll take a closer look at this class of drugs, with particular focus on BESIVANCE®.

BESIVANCE® Indication

BESIVANCE® is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans**, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *Corynebacterium striatum**, *Haemophilus influenzae*, *Moraxella catarrhalis**, *Moraxella lacunata**, *Pseudomonas aeruginosa**, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis**, *Staphylococcus lugdunensis**, *Staphylococcus warneri**, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius**.[3]

** Efficacy for this organism was studied in fewer than 10 infections.*

BESIVANCE®

Fluoroquinolones halt bacterial cell division by binding to and inhibiting the two enzymes essential for DNA replication: DNA gyrase and topoisomerase IV. Differences in binding affinities are most responsible for the variations seen in the minimal inhibitory concentration (MIC) between different drugs. This binding happens only during replication, at which time bacteria are susceptible. To be effective, a drug must be present at high enough concentrations and for long enough duration to catch the cells during division. The structure of BESIVANCE® results in a balanced inhibition of these two essential enzymes rather than the preferential inhibition of one or the other enzyme, as seen in some other ocular fluoroquinolones.[4] Therefore, two mutations are necessary for the bacteria to develop resistance to BESIVANCE®.

Additionally, the vehicle in which BESIVANCE® is suspended, DuraSite (InSite Vision), is designed to extend drug retention in the tear film and allows for sustained concentrations much higher than the MIC against common ocular pathogens. Peak tear concen-

Important Risk Information for BESIVANCE®

- BESIVANCE® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.
- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- BESIVANCE® is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
- Safety and effectiveness in infants below one year of age have not been established.

Please see the full prescribing information for BESIVANCE® on page 3.

trations of BESIVANCE® are 1,200 to 10,000 times greater than the MIC_{90} for key ocular pathogens (*S. epidermidis*, *S. aureus*, *S. pneumoniae* and *H. influenzae*).[5] The dual-halogenated structure of BESIVANCE®, with a novel chlorine group at C8 and aminoazepinyl group at C7, provides for good potency and broad-spectrum activity against Gram-positive and Gram-negative bacteria.

BESIVANCE® is supplied as a 7.5-mL bottle filled with 5 mL of besifloxacin ophthalmic suspension, 0.6%. The recommended initial dose is one drop in the affected eye(s) t.i.d., four to 12 hours apart for seven days. BESIVANCE® is the topical antibiotic I prescribe for bacterial conjunctivitis because of its low resistance profile, clinical efficacy, safety and flexible dosing regimen. Let's take a look at what the clinical trials have shown.

Clinical Data

The FDA approval of BESIVANCE® was based on a series of clinical trials. In a randomized, double-masked, vehicle-controlled, multicenter clinical trial that enrolled subjects one year old and older who had bacterial conjunctivitis. Subjects were treated t.i.d. for five days with BESIVANCE® (n=198) or vehicle (DuraSite, n=191), and BESIVANCE® was found to be superior to the vehicle; clinical resolution was achieved in 45% of the BESIVANCE®-treated group vs. 33% of the vehicle-treated group (difference 12%, 95% CI 3% to 22%). Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 91% for the BESIVANCE®-treated group vs. 60% for the vehicle-treated group (difference 31%, 95% CI 23% to 40%).[6] Additionally, only 9.2% of eyes receiving besifloxacin experienced adverse events, compared with 13.9% of eyes receiving vehicle.[6]

These results were confirmed in a separate multicenter, prospective, randomized, double-masked, vehicle-controlled, parallel-group study. Patients with culture-confirmed bacterial conjunctivitis received topical besifloxacin ophthalmic suspension 0.6% (n=60) or vehicle (n=58) t.i.d. for five days. By day eight, 73.3% of the patients in the besifloxacin group and 43.1% of the patients in the vehicle group had clinical resolution of the infection.[7] Approximately half of the patients in both groups (50.4% in the besifloxacin group and 53.0% in the vehicle group) experienced adverse events (eye pain, blurred vision and eye irritation) that were graded mild or moderate in severity.[7]

Another study compared besifloxacin to moxifloxacin for the treatment of bacterial conjunctivitis. In it, 1,161 patients who were 1 year or older and who had bacterial conjunctivitis were randomized to receive either besifloxacin or moxifloxacin t.i.d. for five days. By day five, 58.3% of the patients in the besifloxacin group and 59.4% of the patients in the moxifloxacin group had clinical resolution of the infection, and 93.3% and 91.1%, respectively, had microbial eradication.[8] On day eight, 84.5% of patients in the besifloxacin group and 84.0% of those in the moxifloxacin group had clinical resolution, and 87.3% and 84.7%, respectively, had eradication of bacteria.[8] While both drugs were well tolerated, eye irritation occurred more often in eyes in the moxifloxacin group (0.3% vs. 1.4%).[8] The researchers concluded that besifloxacin provided similar safety and efficacy to moxifloxacin.[8]

Antibiotic Resistance

One of the important things to consider when treating bacterial conjunctivitis is emerging drug resistance patterns. MRSA and MRSE are of increasing concern.[9] The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study compiled antibiotic susceptibility trends in ocular isolates.[10] Among fluoroquinolones, besifloxacin had the lowest MIC_{90} (4 µg/mL compared to 32 µg/mL for moxifloxacin and 256 µg/mL for ciprofloxacin) against methicillin-resistant staphylococcal ocular isolates.

Conclusion

When choosing a topical antibiotic in the setting of bacterial conjunctivitis, it is important to consider typical pathogens and antibiotic-resistance patterns. BESIVANCE® has a broad-spectrum Gram-positive and Gram-negative coverage for common ocular pathogens. Low MICs, including against MRSA and MRSE, and extended ocular contact provided by the mucoadhesive vehicle DuraSite make BESIVANCE® an excellent choice for empiric treatment of bacterial conjunctivitis. I have found this drug to be an important addition to my treatment armamentarium in the setting of this condition.

Patient Case Example

An 82-year-old woman with Alzheimer's dementia presented to my clinic with a history of redness, irritation and yellow mucoid discharge in both eyes. She currently lived in a nursing care facility and had waxing and waning symptoms of bacterial conjunctivitis. At the time of presentation, she was being treated intermittently and ineffectively with topical lubricating drops and generic antibiotics prescribed 'as needed'.

On examination, she had bilateral grade 3 lower lid ectropion with severe superficial punctate keratitis, mucoid yellow discharge and 3+ papillary reaction in the tarsal conjunctiva in both eyes. I obtained a culture specimen from the inferior cul de sac and prescribed BESIVANCE® (besifloxacin ophthalmic suspension 0.6%, Bausch + Lomb) t.i.d. OU, along with aggressive lubrication with artificial tears.

The culture grew methicillin-resistant *Staphylococcus aureus* (MRSA) and at the one-week follow-up visit, the discharge was no longer present and papillary change was significantly improved. Continued topical lubrication and ointment at bedtime was advised, along with the future surgical treatment of her bilateral ectropion.

Dr. McCabe received her medical degree from the Medical College of Wisconsin and completed her residency training at the Bascom Palmer Eye Institute of the University of Miami's School of Medicine. Recently, she has successfully fulfilled the requirements for Maintenance of Certification to be recertified as a Diplomate of the American Board of Ophthalmology.

1. Smith AF, Waycaster C. Estimate of the direct and indirect annual cost of bacterial conjunctivitis in the United States. BMC Ophthalmol. 2009;9:13.
2. Asbell PA, Sahm DF, Shaw M, Draghi DC, Brown NP. Increasing prevalence of methicillin resistance in serious ocular infections caused by Staphylococcus aureus in the United States: 2000 to 2005. J Cataract Refract Surg. 2008;34:814-818.
3. BESIVANCE® package insert. Tampa, FL: Bausch & Lomb Incorporated; 2012.
4. Cambau E, Matrat S, Pan X, et al. Target specificity of the new fluoroquinolone besifloxacin in Streptococcus pneumoniae, Staphylococcus aureus, and Escherichia coli. J Antimicrob Chemother. 2009;63(3):443-50.
5. Data on file, Bausch & Lomb Incorporated.
6. Tepedino ME, Heller WH, Usner DW, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. Curr Med Res Opin. 2009;25(5):1159-69.
7. Karpecki P, Depaolis M, Hunter JA, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: A multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. Clin Ther. 2009;31(3):514–526.
8. McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009;116:1615–1623.
9. Muckley E. Are we gaining ground on ocular infection? Rev Optom. 2012; Dec 15:36–40.
10. Haas W, Pillar CM, Torres M, Morris TW, Sahm DF. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. Am J Ophthalmol. 2011;152(4):567–574.

BAUSCH+LOMB

Besivance®

besifloxacin ophthalmic suspension, 0.6%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Besivance safely and effectively. See full prescribing information for Besivance.

Besivance® (besifloxacin ophthalmic suspension) 0.6%
Sterile topical ophthalmic drops
Initial U.S. Approval: 2009

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1) 09/2012

---------- INDICATIONS AND USAGE ----------

Besivance® (besifloxacin ophthalmic suspension) 0.6%, is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:
*Aerococcus viridans**, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *Corynebacterium striatum**, *Haemophilus influenzae, Moraxella catarrhalis**, *Moraxella lacunata**, *Pseudomonas aeruginosa**, *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis**, *Staphylococcus lugdunensis**, *Staphylococcus warneri**, *Streptococcus mitis* group, *Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius**
*Efficacy for this organism was studied in fewer than 10 infections. (1)

---------- DOSAGE AND ADMINISTRATION----------

Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days. (2)

---------- DOSAGE FORMS AND STRENGTHS----------

7.5 mL size bottle filled with 5 mL of besifloxacin ophthalmic suspension, 0.6% (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS ----------

Topical Ophthalmic Use Only. (5.1)

Growth of Resistant Organisms with Prolonged Use. (5.2)

Avoidance of Contact Lenses. Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance. (5.3)

---------- ADVERSE REACTIONS----------

The most common adverse reaction reported in 2% of patients treated with Besivance was conjunctival redness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Besivance® (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:
*Aerococcus viridans**
CDC coryneform group G
*Corynebacterium pseudodiphtheriticum**
*Corynebacterium striatum**
Haemophilus influenzae
*Moraxella catarrhalis**
*Moraxella lacunata**
*Pseudomonas aeruginosa**
Staphylococcus aureus
Staphylococcus epidermidis
*Staphylococcus hominis**
*Staphylococcus lugdunensis**
*Staphylococcus warneri**
Streptococcus mitis group
Streptococcus oralis
Streptococcus pneumoniae
*Streptococcus salivarius**
*Efficacy for this organism was studied in fewer than 10 infections.

2 DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once before use.

Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

3 DOSAGE FORMS AND STRENGTHS

7.5 mL bottle filled with 5 mL of besifloxacin ophthalmic suspension, 0.6%.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

NOT FOR INJECTION INTO THE EYE.

Besivance is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

5.2 Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of Besivance (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

5.3 Avoidance of Contact Lenses

Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

6 ADVERSE REACTIONS

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

The data described below reflect exposure to Besivance in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported ocular adverse reaction was conjunctival redness, reported in approximately 2% of patients.

Other adverse reactions reported in patients receiving Besivance occuring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean C_{max} in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day (C_{max}, 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.

Since there are no adequate and well-controlled studies in pregnant women, Besivance should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Besifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance is administered to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of Besivance® in infants below one year of age have not been established. The efficacy of Besivance in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials *[see CLINICAL STUDIES (14)]*.

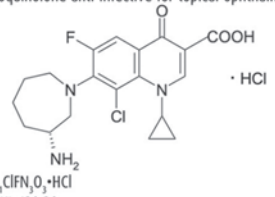
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

Besivance (besifloxacin ophthalmic suspension) 0.6%, is a sterile ophthalmic suspension of besifloxacin formulated with DuraSite®† (polycarbophil, edetate disodium dihydrate and sodium chloride). Each mL of Besivance contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.



$C_{19}H_{21}ClFN_3O_3 \cdot HCl$
Mol Wt 430.30

Chemical Name: (+)-7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1- cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

Besifloxacin hydrochloride is a white to pale yellowish-white powder.

Each mL Contains:
Active: besifloxacin 0.6% (6 mg/mL);
Preservative: benzalkonium chloride 0.01%
Inactives: polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection.

Besivance is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Besifloxacin is a fluoroquinolone antibacterial *[see CLINICAL PHARMACOLOGY (12.4)]*.

12.3 Pharmacokinetics

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received Besivance bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL. The mean besifloxacin C_{max} was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.

12.4 Microbiology

Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycoside, macrolide, and β-lactam antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. *In vitro* studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

In vitro resistance to besifloxacin develops via multiple-step mutations and occurs at a general frequency of $< 3.3 \times 10^{-10}$ for *Staphylococcus aureus* and $< 7 \times 10^{-10}$ for *Streptococcus pneumoniae*.

Besifloxacin has been shown to be active against most isolates of the following bacteria both *in vitro* and in conjunctival infections treated in clinical trials as described in the INDICATIONS AND USAGE section:

*Aerococcus viridans**, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *C. striatum**, *Haemophilus influenzae, Moraxella catarrhalis**, *M. lacunata**, *Pseudomonas aeruginosa**, *Staphylococcus aureus, S. epidermidis, S. hominis**, *S. lugdunensis**, *S. warneri**, *Streptococcus mitis* group, *S. oralis, S. pneumoniae, S. salivarius**

*Efficacy for this organism was studied in fewer than 10 infections.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.

No *in vitro* mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.

Besifloxacin induced chromosomal aberrations in CHO cells *in vitro* and it was positive in an *in vivo* mouse micronucleus assay at oral doses ≥ 1500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

14 CLINICAL STUDIES

In a randomized, double-masked, vehicle controlled, multicenter clinical trial, in which patients 1-98 years of age were dosed 3 times a day for 5 days, Besivance was superior to its vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 45% (90/198) for the Besivance treated group versus 33% (63/191) for the vehicle treated group (difference 12%, 95% CI 3% - 22%). Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 91% (181/198) for the Besivance treated group versus 60% (114/191) for the vehicle treated group (difference 31%, 95% CI 23% - 40%). Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

Besivance® (besifloxacin ophthalmic suspension) 0.6%, is supplied as a sterile ophthalmic suspension in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and tan polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.

5 mL in 7.5 mL bottle
NDC 24208-446-05

Storage:

Store at 15°-25°C (59°-77°F). Protect from Light. Invert closed bottle and shake once before use.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other source.

Although Besivance is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Besivance or other antibacterial drugs in the future.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

Patients should be advised to thoroughly wash hands prior to using Besivance.

Patients should be instructed to invert closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated
Tampa, Florida 33637

Besivance® is a registered trademark of Bausch & Lomb Incorporated.

U.S. Patent Nos. 6,685,958; 6,699,492; 5,447,926

†DuraSite is a trademark of InSite Vision Incorporated

9142605(flat)
9142705(folded)

REVIEW® of Ophthalmology

EDITORIAL STAFF

Editor in Chief
Christopher Glenn
(610) 492-1008
cglenn@jobson.com

Managing Editor
Walter C. Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(814) 861-5559
ckent@jobson.com

Associate Editor
Kelly Hills
(610) 492-1025
khills@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Senior Director, Art/Production
Joe Morris
(610) 492-1027
jmorris@jobson.com

Art Director
Jared Araujo
(610) 492-1023
jaraujo@jobson.com

Graphic Designer
Matt Egger
(610) 492-1029
megger@jobson.com

International coordinator, Japan
Mitz Kaminuma
Reviewophthalmo@aol.com

Business Offices
11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States — (877) 529-1746
Outside U.S. — (847) 763-9630
E-mail:
rhsubs@halldata.com
Website: www.revophth.com

Professional Publications Group
Jobson Medical Information LLC

Three Wishes for Long-Overdue Action

There is no cleaner slate, no more hopeful time than January. As I write this, we're closing out the year, when holiday wishes are pervasive. With those two influences in mind, here's a trio of wishes for 2014:

• After 15 temporary patches since 2003, at a cost that some have put at $150 billion, may our Congressional leaders finally do away with the mess they created in 1997 with the Sustainable Growth Rate formula for Medicare reimbursement. As always, the legislative situation is fluid and last-minute, with the House approving a three-month delay in the anticipated 20-plus percent cut scheduled for 2014, and the Senate expected to take up the patch this week.

But many in Washington are pointing to more substantive efforts undertaken late this year that culminated on Dec. 12 with both the Senate Finance Committee and the House Ways and Means Committee approving legislation that would permanently repeal the SGR. Another can kicked down the road would not surprise anyone, but many seem confident that the "Value-based Payment Program" that would replace the PQRI and meaningful use programs may finally be the death knell of SGR.

• May this be the year that U.S. surgeons can finally have access to corneal crosslinking. In late November, the FDA granted priority review to Avedro of the new drug application for its crosslinking system. The priority review status establishes a PDUFA date of March 15, 2014. The proposed indications of treatment of keratoconus and corneal ectasia following refractive surgery are both orphan indications, prompting the priority review. With thousand of successful treatments and years of data collected internationally, crosslinking has become the poster boy for what's wrong with the FDA trial system.

• May GSK's announcement regarding changes in its financial relationship with doctor/spokespersons, and in the way it compensates its sales reps, be an inspiration for other pharmaceutical and medical device companies. The company will end the practice of direct payments to health-care professionals for speaking engagements and for attendance at medical conferences. In addition, the company will eliminate individual sales targets for reps. Instead, GSK's sales reps who work directly with prescribing health-care professionals will be "evaluated and rewarded for their technical knowledge, the quality of the service they deliver to support improved patient care and the overall performance of GSK's business," the company said.

Some aspects of the new program are already in practice at other companies. But the overall trend toward transparency of relationships between industry and physicians, and quality, evidence-based education on medical products is to be applauded.


Long-term Noninvasive Topical Drug Delivery

New approaches appear to have the potential to simplify patient participation in the delivery of ocular medications.

Christopher Kent, Senior Editor

Ophthalmologists have long awaited an effective means to deliver topical drugs with minimal patient participation. Here, two groups of researchers describe their work developing two different noninvasive drug delivery methods that really do appear to work.

A Drug-Eluting Contact Lens

For many years researchers have attempted to create a contact lens that, in addition to meeting the refractive needs of a patient, would allow a drug to gradually seep out onto (and into) the eye for an extended period of time. This turned out to be difficult.

One team that has made major headway along these lines is a group in Boston, led by Daniel S. Kohane, MD, PhD, professor of anaesthesia and director of the Laboratory for Biomaterials and Drug Delivery at Harvard Medical School, and Joseph B. Ciolino, MD, at Harvard Medical School and the Massachusetts Eye and Ear Infirmary. Their team has developed a contact lens that elutes a drug at a consistent level for—in some cases—months, in *in vivo* studies using rabbits.

Dr. Kohane explains. "People have been trying to create something like this for decades," he says. "In most cases, the results have allowed release of a drug for several hours or a day. In contrast, our lens has been shown, *in vitro*, to be capable of releasing substantial amounts of a drug over a period of months with relatively constant kinetics, so the same amount is released every day."

Dr. Kohane says that the lens they've developed is a bit like a sandwich. "There are two layers of hydrogel material similar to a standard contact lens," he says. "In between those layers is a flat doughnut that's made of a polymer containing a drug. The hole in the doughnut overlies the pupil so you can see through it."

Dr. Kohane notes that several things enable the lens to be effective for multiple months. "First of all," he says, "this is local therapy and the drugs we're testing tend to be very potent. Second, the polymer doughnut is a macroscopic object, which means we can pack a lot of drug into it—more than any other device that I'm aware of. That, and the specific polymeric composition of the material that allows the slow and even release of the drug account for our success."

Controlled Release

Dr. Kohane explains that the drug is eluted through a combination of drug diffusion and biocompatible polymer degradation. "When we tested the system with an antibiotic, we found that the drug was still being released evenly at three months, as documented in a paper we published at the time.[1] We also tried the lens with econazole, an antifungal, and it was still working at three weeks. Our most recent study used latanoprost, a glaucoma medication, and we got good steady-state release and penetration into the anterior chamber for a month, which we measured by doing serial fluid withdrawals from the anterior chamber.[2] We've tried this with both hydrophilic and hydrophobic drugs, and both worked."

Dr. Kohane says the speed at which the drug is released can easily be altered. "There are lots of parameters you can play with to get the release characteristics you want, including

the ratio of polymer to drug, the nature of the polymer and the thickness of the polymer film," he says. He adds that biocompatibility has not been a problem so far, although human testing will be necessary to confirm that this extends to people.

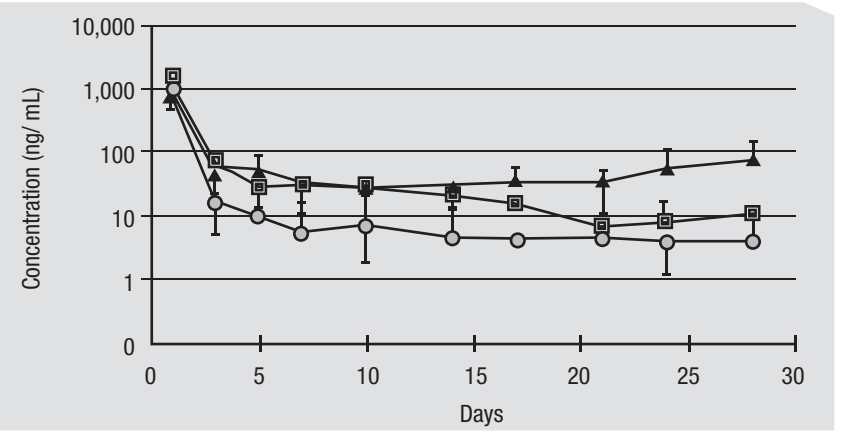
The shelf life of the lens prior to use will depend on the specific structure of the lens and the drug that's encapsulated in it. "It also depends on whether the lens is freeze-dried before delivery, in which case the user would reconstitute it in fluid before putting it on for the first time," Dr. Kohane notes. "Our preliminary data suggest that wet or dried, the shelf life would be reasonable. Freeze-drying the lens doesn't appear to damage it or affect its performance. The issue with storing it in a wet state is the possibility of continued drug release during storage, but that could be controlled by packaging it in a very confined space in a solution that already contains the drug."

Trials with dogs and non-human primates have already begun. "As those trials wind down we'll start lining up human trials," he says.

A High-Tech Eye Drop

Another promising approach to long-term drug delivery is under development at the University of Pittsburgh McGowan Institute for Regenerative Medicine and UPMC Eye Center in Pittsburgh. In this technology, drug-imbued microspheres are embedded in a reverse-thermal gel liquid that becomes a flexible, shape-conforming solid when it reaches body temperature. The patient can place a drop of the gel in the fornix, where it remains for an extended period while the microspheres slowly elute their drug content. The research, being conducted by Morgan V. Fedorchak, PhD, Steven R. Little, PhD, Ian Conner, MD, PhD and Joel S. Schuman, MD, is showing promise as a means to circumvent issues of patient adherence. (The University of Pittsburgh has applied for a patent.)

Drug-Eluting Lenses: Latanoprost Levels in Aqueous Humor



Three variations in lens parameters produced different aqueous levels of latanoprost over time in rabbit eyes. For comparison, the average concentration over 24 hours was about 12 mg/ml using topical drops. (Chart based on *Ciolino et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials 2014;35:1:432-9.*)

"Using a rabbit model, we found that if we injected the microspheres subconjunctivally they provide IOP reduction for as long as a month," says Dr. Schuman. "When I heard about the reverse-thermal gel I wondered whether we could combine the gel with the microspheres to circumvent the need for the injection. It turns out this works just fine, so we switched from injecting the microspheres to putting them in the gel. The substance comes out of the bottle as a drop; it warms up against the eye and becomes a flexible solid that conforms to the shape of the fornix, where it can remain as long as necessary. We've tested drug delivery lasting a month, but that length of time could be made shorter or longer as necessary.

"Our goal is to be able to enhance adherence to therapy by giving patients the ease of just taking a drop once a month instead of multiple times," he continues. "Having the drug available as an eye drop should eliminate some of the problems we saw with the Ocusert device many years ago. The drug we tested in this case was brimonidine, but you could have any drug in this vehicle. This technology should allow a patient to undergo treatment for a long period of time with minimal effort, which we believe will enhance the effectiveness of treatment."

Dr. Schuman notes that eye rubbing shouldn't be a problem. "We haven't tested the device in a human cohort yet, but there's no reason to think this would be a concern," he says. "This approach might be contraindicated if a patient constantly rubs his eyes, but generally that should not be a problem.

"Right now we're testing it in animals and it's working great," he adds. "Of course, lots of things work in animals that don't work in humans, so we're keeping our expectations realistic. But we're very hopeful, because the studies so far have given us a lot to be encouraged about. Next, we'll most likely be looking to file with the FDA." REVIEW

1. Ciolino JB, Hoare TR, Iwata NG, Behlau I, Dohlman CH, Langer R, Kohane DS. A drug-eluting contact lens. Invest Ophthalmol Vis Sci 2009;50:7:3346-52.
2. Ciolino JB, Stefanescu CF, Ross AE, Salvador-Culla B, Cortez P, Ford EM, Wymbs KA, Sprague SL, Mascoop DR, Rudina SS, Trauger SA, Cade F, Kohane DS. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials 2014;35:1:432-9.

Toric IOLs: More Options, More Patients

Christopher Kent, Senior Editor

The expanding array of toric intraocular lenses available in the Unites States is spurring increasing use of these lenses.

As most ophthalmologists know, surgeons outside the United States have access to many more toric intraocular lenses than surgeons in the United States. That situation, however, is gradually starting to change; currently, American surgeons are able to choose between four toric options.

Here, experienced surgeons offer their opinions on the advantages of the toric lenses currently available, and advice for getting optimum results when implanting them.

Surveying the Options

The first toric option approved in the United States, still in use, was the STAAR single-piece plate toric IOL. However, the AcrySof toric IOL has become many surgeons' go-to toric lens in recent years; reported good outcomes and an increasing range of power options—as well as having been the only toric IOL with haptics for a number of years—have made it the leading option.

More recently, two new toric IOLs have become available: the Tecnis toric from Abbott Medical Optics and the Trulign toric from Bausch + Lomb, the latter created on the Crystalens platform.

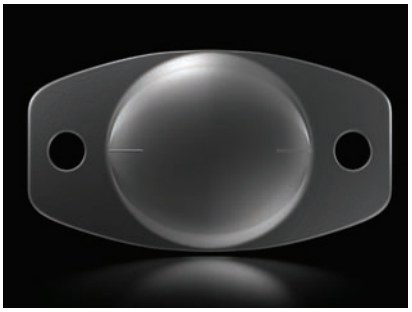
Douglas D. Koch, professor of ophthalmology at Baylor College of Medicine in Houston, was involved in the clinical trials of the Tecnis toric and has worked with the Tecnis lens for about three years. "I like the Tecnis a lot," he says. "There are many similarities between the AcrySof and Tecnis torics; they're both on a single-piece, hydrophobic platform and they're both terrific lenses. They differ in that the Tecnis is clear, not yellow, and it has a little more negative spherical aberration and less chromatic aberration.

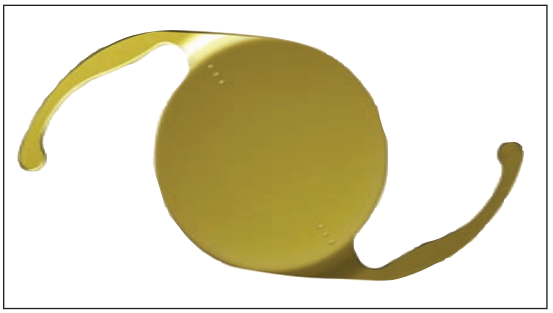
"The Tecnis comes in four powers that correct 1, 1.5, 2 and 2.75 D of astigmatism at the corneal plane," he continues. "For now, the AcrySof has the advantage in terms of the wider range of available powers. The Tecnis material is hardy and doesn't easily scratch. It also has a lower refractive index and lower reflectivity so that it's not cosmetically noticeable when people look at someone who has the implant. The vast majority of patients don't care about this, but every once in a while it comes up. On the other hand, the Alcon lens has a full 6-mm refractive optic. Overall, I like both lenses a lot."

Dr. Koch notes one difference when implanting the Tecnis. "The lens is a little different going in because you can rotate it easily in either

This article has no commercial sponsorship.

direction when you're trying to position it," he says. "Because it's very flexible and the haptics are a little less sticky than the Alcon lens, you can actually back-rotate it, which is a nice feature. I wouldn't try to back-rotate it 90 degrees, but you can go back 20 degrees or so if you need to."





The STAAR single-piece toric plate IOL (above) was the first toric approved in the United States. Alcon's AcrySof (right) was the first with haptics, helping to spread the popularity of this type of correction.

Terry Kim, MD, professor of ophthalmology at Duke University Eye Center in Durham, N.C., has been using the Trulign toric. "The Trulign will allow us to reduce cylinder in patients who are looking to get more range of vision with the Crystalens," he notes. "I think that's important, because whether you're talking about a multifocal or accommodating lens, we all know that astigmatism can adversely affect outcomes. Until now, when we implanted these lenses we had to treat astigmatism with a limbal relaxing incision or astigmatic keratotomy, and these incisions just aren't that accurate, especially when correcting more than 2 D of astigmatism. So having the ability to treat astigmatism built into a lens like the Crystalens is a welcome addition. It will reduce cylinder and improve results."

Dr. Kim notes that the Trulign doesn't seem to rotate much postoperatively. "One thing that I've found with this platform is that it does stay where you put it at the end of the case," he says. "That's one of the keys to success with any toric IOL; you don't want intraoperative or postoperative rotation.

"With a single-piece Tecnis or AcrySof toric IOL, I advocate going behind the lens with the irrigation/aspiration tip to aspirate all of the viscoelastic out of the bag, because any residual viscoelastic between the lens and the capsule could allow potential lens rotation intraoperatively or postoperatively," he continues. "With the Trulign that's not as much of an issue because you can do the 'rock and roll' technique, where you tilt the lens to its side using the I/A tip to burp out the viscoelastic behind the lens."

As noted, the STAAR one-piece silicone plate toric IOL is still in use by many ophthalmologists as well. "The single-piece plate toric is less popular than some others," notes Nick Mamalis, MD, professor of ophthalmology at the Moran Eye Center, University of Utah, in Salt Lake City. "One issue is that the fit in the capsular bag is not as predictable as it is with a lens that has haptics. That makes sizing important. If you have an eye with a very large capsular bag, such as a myopic eye, then you might need a slightly larger lens to get a good fit and prevent rotation. To address that, the toric from STAAR comes in two widths: 10.8 mm and 11.2 mm. The other issue is that the STAAR toric is made of silicone. When a broad plate of silicone has contact with the anterior capsule you can get anterior capsular fibrosis and opacification."

"I haven't used the STAAR one-piece lens lately, just because my results with the AcrySof toric have been so outstanding," says Stephen S. Bylsma, MD, who practices at Shepard Eye Center in Santa Maria, Calif., and is a faculty member at UCLA Department of Ophthalmology, affiliated with Jules Stein Eye Institute. "The AcrySof is very stable in the eye and has a wide range of astigmatism-correcting powers. However, the STAAR plate format does have some advantages. Some torics can cause a 'cat eye' reflection that can be observed by someone else. I've had patients who have noticed it in others, and they specifically request that they not have that effect. In those cases I use the STAAR lens. Also, there are no glistenings in the STAAR lenses, because the lens material is different."

Lenses vs. Incisions

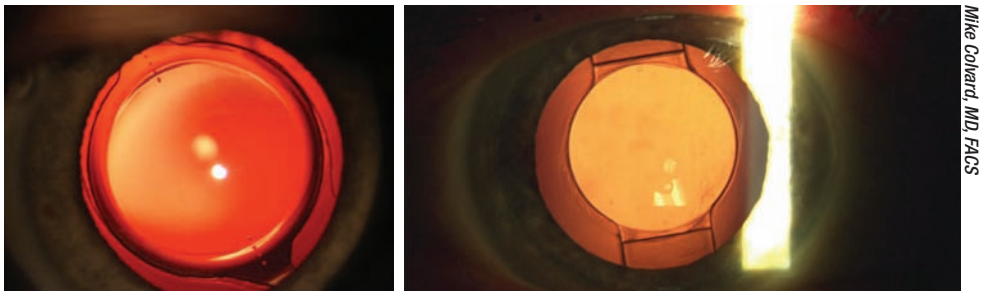
Despite the weaknesses inherent in correcting astigmatism with manual incisions, the advent of femtosecond-laser-created corneal incisions has raised the possibility that these more precise incisions might make corrections on a par with toric IOLs.

Nevertheless, toric IOLs still have some significant advantages. "The issue for me has always been one of optically correcting astigmatism rather than using tissue manipulation," says Dr. Bylsma. "Correcting astigmatism with an IOL is much more accurate. To not have to do LRIs along with the Crystalens, for example, is a big advance."

"A toric IOL helps to save tissue and creates cleaner optics," agrees Dr. Mamalis. "I generally only use LRIs now for very small amounts of astigmatism. If the patient has a greater degree of astigmatism than we're able to correct optically, that patient would require an additional tissue procedure such as PRK, LASIK or an LRI, depending on

the amount. In that situation we debulk the astigmatism with the strongest lens we have available; that helps to minimize the amount of tissue correction needed."

Dr. Kim notes that one big advantage of toric IOLs compared to LRIs is that if the axis you choose turns out to be a little off, you have the ability to go back and rotate the lens into the correct axis. "You can't do that with an LRI," he points out. "Once it's done, you cannot undo it. And they have other limitations: Their effect can regress; you can overcorrect or induce irregular astigmatism; and they can lead to complications such as a wound leak or perforation. Treating astigmatism via the IOL is a much more stable and reliable approach."



Mike Colvard, MD, FACS

Recent additions to the toric IOL options include the Tecnis toric (above left) and the Trulign toric, created on the Crystalens platform (above right).

Dr. Kim acknowledges, however, that femtosecond lasers may eventually impact whether surgeons choose to implant a toric IOL. "As you know, femtosecond lasers can create LRI and AK incisions," he says. "They can be very precisely programmed. For instance, when I do an LRI manually I use a 600-µm keratome blade to create a limbal relaxing incision in the peripheral cornea. Like most surgeons, I don't measure the peripheral corneal thickness first, so I never really know if I'm getting down to exactly 90 percent deep, for example. But a femtosecond laser, which takes an OCT image of the cornea, can be programmed to make that incision down to exactly 90 percent depth.

"In addition," he continues, "you can customize the design of the incision, in terms of length, depth and angulation and whether you want it to open all the way to the epithelial surface or not. Furthermore, many surgeons are not actually opening the incisions at the time of surgery; instead, they titrate the effect of the incision by opening it later, as needed, once the patient has stabilized after cataract surgery.

"What we don't know is, how will the wound-healing response compare to that of blade-created LRI incisions?" he continues. "We don't have enough data yet to know how that's going to affect our treatment of astigmatism, and whether these will be better than manual incisions. But femtosecond lasers have definitely opened up another approach to treating corneal astigmatism, and it may eventually impact the manner in which surgeons choose to use torics IOLs."

As to the issue of whether femtosecond-laser-created incisions can produce outcomes as good as a toric IOL, Dr. Mamalis says he'd love to see a good study comparing them. "People are talking about this," he notes, "but I haven't seen a good prospective study looking at it.

"In terms of LRIs made manually, they tend to undercorrect a little bit compared to toric lenses," he adds. "And they don't necessarily offer the patient a cost savings compared to implanting a toric IOL. It's not just the cost of the lens itself that the patient is paying for; it's the extra measurements and work that goes into evaluating the eye preop, as well. We still have to do that work if we're planning to do a limbal relaxing incision. It's true that some doctors don't charge to do LRIs; they just do them automatically. If I'm doing a touch-up, then I won't charge for an LRI. But if I'm doing it as a primary correction, then there is a charge involved."

Making the Most of Torics

The following strategies can help maximize your success with torics, whether you're implanting the newer or older approved lenses.

• ***Offer the toric IOL option to all patients with astigmatism.*** "Insurance and Medicare do not cover these lenses, so patients have to pay for them out of pocket," Dr. Mamalis points out. "Obviously, not all patients will have the resources to afford a toric lens. However, you don't want to prejudge and assume someone can't afford it.

"Whenever a patient has significant astigmatism, regardless of appearances, I let him know that we do have an implant available that can correct that, although he'll have to cover the cost himself," he continues. "If that's not feasible, we can correct his astigmatism afterwards with eyeglasses, as he's most likely already doing. Always give everyone the option and let them make the decision."

• ***Take topography measurements before doing tonometry or putting in dilating drops.*** "If a patient comes in with a cataract, we do the topography prior to dilating or measuring IOP because both drops and tonometry can disturb the surface of the eye and make our topography measurements less accurate," says Dr. Mamalis. "We do the topography measurements on a virgin cornea. If we realize that the topography was inadvertently not done first, we have the

patient come back later for a second measurement. It's really important to get the most accurate topography possible."

• ***Don't rely on a single measurement source.*** Dr. Mamalis says he relies on at least two instruments to make his preoperative astigmatic measurements. "The IOLMaster is pretty good at picking up the axis of astigmatism," he notes. "But for the magnitude of the astigmatism, I find that corneal topographers give you more accuracy."

Dr. Bylsma also says he uses a combination of topography and keratometry to determine his preoperative measurement. "We do automated keratometry at the screening," he explains. "Then we use corneal topography to further analyze the shape of the cornea. We also have the keratometry that comes with the preoperative A-scan done by the IOLMaster or Lenstar, both of which are excellent tools. We look at all of those and make our judgment based on how much they agree.

"Generally they agree very well," he adds. "But again, none of this takes into account any posterior corneal astigmatism, which can lead to a less-than-perfect correction despite careful preop measurements."

• ***When the measured astigmatism is halfway between available lens powers, choose carefully.*** Dr. Bylsma says that in this situation he will generally choose the weaker power lens. "We don't want to flip the astigmatism axis," he says. "Patients are used to their own astigmatism; they've had it all their lives. As long as we reduce it significantly and leave it in the same axis, they're very happy. But if we give them a new axis of astigmatism by overcorrecting their previous astigmatism, they can be very unhappy; they're not used to the distortion being in the new direction."

Dr. Mamalis says his choice of which way to go depends on the axis. "Dr. Koch has been doing a lot of work on posterior corneal astigmatism, showing that it's important to take that into account, if possible," he explains. "One of the things he has shown is that this is related to whether the anterior astigmatism is with-the-rule or against-the-rule.[1] Based on his research, if the patient has with-the-rule astigmatism, I will tend to choose the less powerful lens, assuming the anterior measurement falls in between lens powers. If it's against-the-rule astigmatism, I will choose the step up rather than down." (Dr. Koch's nomogram is shown in the table on p. 25.)

• ***If a patient with very low ATR astigmatism has a correction for that in his spectacles, a toric lens is a good choice.*** "Even if the amount of ATR astigmatism you measure is small, say 0.4 D, if the patient has a

Intraoperative Aberrometry and Toric IOLs: Perfect Together?

Given the importance of positioning the toric IOL as precisely as possible, the recent development of instruments allowing the surgeon to check the patient's aphakic refraction on the operating table is a noteworthy advance.

Stephen S. Bylsma, MD, a faculty member at UCLA's Department of Ophthalmology, says he has a lot of experience with the ORA intraoperative aberrometer (WaveTec Vision). "This is probably the biggest breakthrough after the IOLs themselves, in terms of being able to account for exact alignment of the IOLs," he says. "Using the reticule on the ORA definitely increases the postop uncorrected visual acuity in patients receiving toric IOLs. At this point, I would not put in a toric IOL—or even do an LRI—without using the ORA.

"The main issue with astigmatism is that when the patient goes from sitting upright to lying down, cyclotorsion generally occurs, and it's a variable amount," he continues. "Up until recently, marking patients while sitting upright was used to address that. However, that's still an approximation because astigmatism is typically measured on the anterior cornea with keratometry. None of that accounts for posterior astigmatism. The ORA is a tremendous leap forward because it measures the refraction in the aphakic state, after the cataract has been removed and before the IOL goes in, accounting for the posterior cornea as well as the anterior cornea and the induced astigmatism. As a result, our ability to determine the most effective axis and magnitude of astigmatism correction is more accurate.

"Some surgeons who use the ORA recheck the refraction and adjust the IOL after it's in place," he adds. "I choose not to do that extra step. In my experience it's not necessary. I've gotten outstanding results without doing that."

Despite recommending the ORA, Dr. Bylsma notes that, like all technology, it's not perfect. "It's generally quite reliable and accurate, but there are always those very few cases where you look at what the instrument says and think, 'This is not the result I was expecting.' If that happens, we look at all the information available—keratometry, topography, refraction and ORA—and make the best estimate of what lens power to use. In this situation, I would definitely repeat the ORA after the IOL is placed."

Many surgeons, however, are quick to point out that you can get very good results without having to depend on intraoperative aberrometry. "If you're properly marking the eye and measuring ahead of time, and properly putting in the implant, you'll be successful in the vast majority of patients," says Nick Mamalis, MD, professor of ophthalmology at the Moran Eye Center, University of Utah, in Salt Lake City. "If you're a practitioner without intraoperative aberrometry or a preop registration system, so long as you're using the traditional methods carefully and accurately, you can still get very good results and get very close to the ideal placement of the lens."

—CK

correction for that in his glasses, that's a pretty good indication that there's some ATR power on the back surface of the cornea," notes Dr. Koch. "If you don't provide any correction for that seemingly small amount of astigmatism, that 0.4 could end up being 0.8 postoperatively, and the patient will be unhappy with his quality of vision. In those instances, I recommend a toric lens."

• ***Have a printout of your axis-calculator results in the OR where you can see it during surgery.*** "All toric IOL companies have Web-based axis calculators that are user-friendly," notes Dr. Kim. "I recommend making a printout of the result and having that printout taped to the wall or on your microscope. It's very easy to accidentally align the lens in the wrong axis; having the printout visible helps ensure that you get the orientation right the first time."

Dr. Mamalis agrees that this is a helpful strategy. "I line the printout up exactly as the eye is aligned through the microscope, just as a final check to make sure we're putting the lens in the right place," he says.

• ***When implanting a Trulign, insert the mouth of the inserter all the way into the anterior chamber.*** "The Trulign lens is on the Crystalens AO platform, so if you've been implanting the Crystalens AO, this procedure will be similar," comments Dr. Kim. "If you're not familiar with this platform, I advise enlarging your smaller incision to 3 mm in order to make room for the lens and the cartridge. Then, to insert either the Crystalens or the Trulign, I recommend using the Crystalsert Delivery System, and making sure that the mouth of the cartridge is all the way into the anterior chamber—as opposed to just using what's called 'wound-assisted delivery,' where the mouth of the cartridge just sits in the incision itself.

"The reason is that, unlike a single-piece acrylic lens, which tends to have a gummy consistency and open slowly, this is a silicone lens which can open up pretty quickly," he continues. "If the mouth of the cartridge is all the way into the anterior chamber, you can use a Sinskey hook through the paracentesis incision with your other hand to control the delivery of the Trulign lens into the capsular bag. The lens is very flexible, so control is important. Because of the unique haptic configuration, you want to make sure that the lens's leading haptic goes into the bag.

"I think we automatically tend to tell our toric patients that we're aiming for distance vision only, and they'll still need reading glasses. But it's worth remembering that monovision is also an effective option with these IOLs."
— Terry Kim, MD

"Another issue is that sometimes the trailing haptic will not fully go into the bag," he adds. "If the mouth of the cartridge is all the way in, you can make sure that the haptics are at least in the anterior chamber. Then when you pull the cartridge out, you can position the trailing haptics with a Sinskey hook into the capsular bag."

• ***Remember that the Trulign can be rotated in either direction.*** "When implanting the Trulign, I use what I call a push-and-pull technique, done with a Sinskey hook," explains Dr. Kim. "Unlike the conventional single-piece acrylic toric IOL platforms, where you have to rotate the lens clockwise to get it to the axis that you want, you can rotate the Trulign clockwise or counterclockwise by pushing and pulling on the haptic-optic junction on the IOL until the lens reaches the desired axis. That's because the haptic configuration is balanced; it's symmetric on both sides." (The Tecnis toric can also be back-rotated, although to a lesser degree, as noted earlier.)

• ***When a lens is misaligned, help is on the Web.*** "Occasionally, because of imperfect measurement, imperfect placement or postop lens rotation, the astigmatic axis of a toric IOL will need to be adjusted," says Dr. Kim. "In that situation, you can get help at astigmatismfix.com, a free website created by Minneapolis surgeon David Hardten, MD, and Sioux Falls, S.D. surgeon John Berdahl, MD. If the spherical equivalent of your refractive result is close to plano, it allows you to enter parameters such as the manifest refraction, toric lens model and axis of position, and tells you what the correct optimal position of the toric IOL should be and what refraction the corrected axis will give you. It's a very helpful tool to use if you need to realign a toric IOL." (Dr. Berdahl confirms that the nomogram at astigmatismfix.com will work for the newer toric IOLs as well as the older toric options; all the lens options are available on the website.)

• ***Don't forget about monovision.*** "If you don't want to go with a lens like the Trulign that extends range of vision, you can still do monovision with a toric IOL and have very good results," notes Dr. Kim. "I generally reserve this for patients who are wearing contact lenses with monovision who are already used to it, but the results can be excellent. I think we automatically tend to tell our toric IOL patients that

Baylor Nomogram: Accounting for Posterior Corneal Curvature

Toric IOL correction	With-the-rule (D)	Against-the-rule (D)
0	≤1.69 (PCRI if >1.00)	≤0.39
1	1.70 – 2.19	0.40* - 0.79
1.5	2.20 – 2.69	0.80 – 1.29
2	2.70 – 3.19	1.30 – 1.79
2.5	3.20 – 3.69	1.80 – 2.29
3	3.80 – 4.29	2.30 – 2.79
3.5	4.30 – 4.89	2.80 – 3.29
4	≤4.90	3.30 – 3.79

* especially if the patient's spectacles have had more ATR correction
PCRI = peripheral corneal relaxing incision

Work done by Douglas D. Koch, professor of ophthalmology at Baylor College of Medicine in Houston, and colleagues has demonstrated the importance of taking posterior corneal astigmatism into account when determining the power and axis of astigmatism to correct. The table above offers a generic formula for toric IOL power that can be applied when an exact posterior corneal surface measurement isn't available.

we're aiming for distance vision only, and they'll still need reading glasses. But it's worth remembering that monovision is also an effective option with these IOLs."

Dr. Bylsma agrees. "Toric lenses are helpful in this situation," he says, "because monovision only works well if each eye has excellent, clear vision at its respective distance."

The Technology Keeps Coming

A big part of getting toric IOLs to live up to their full promise is getting them perfectly aligned inside the eye. New technologies in the offing should make that ever easier to do.

"Alcon has a reference unit/digital marker system called Verion," notes Dr. Kim. "The reference unit portion will allow you to take an image of the patient's scleral/conjunctival blood vessels and pupil/iris architecture and plan your astigmatism treatment on that, whether it's going to be an LRI/AK incision or a toric IOL. It puts the information on a USB stick that you plug into a device that attaches to

(continued on page 69)

Multifocals: Sweat The Small Stuff

Walter Bethke, Managing Editor

Surgeons share their tips for catching all the elusive problems that could derail a multifocal lens.

An old proverb warns, "For want of a nail, the kingdom was lost," and reminds us how a small oversight can create ripples that cause huge problems. Surgeons who implant multifocal intraocular lenses can be subject to similar forces, and they say small aspects of the ocular anatomy, or the surgery itself, can touch off shock waves that knock the outcome off kilter. Here, doctors who perform the procedure or evaluate prospective multifocal-lens patients preop describe how to catch these small flaws and deal with them before they can have an effect.

Preop Issues

Experts say that, when looking for potential problems, their evaluation runs the gamut from a patient's cornea and retina to his personality.

• ***Age.*** Surgeons say something as basic as a person's age can affect the outcome of a multifocal. "One of the aspects is just age in general," says Des Moines, Iowa, ophthalmologist James Davison. "We don't have a hard-and-fast age limit, but if someone frail comes in wanting the best vision but isn't in shape to appreciate the function of the multifocal intraocular lens, we kind of discourage it in him. With these IOLs, there is some loss of contrast sensitivity, and you need a certain mental facility to enjoy the kind of vision multifocals give you. Some people just don't have that mental facility anymore."

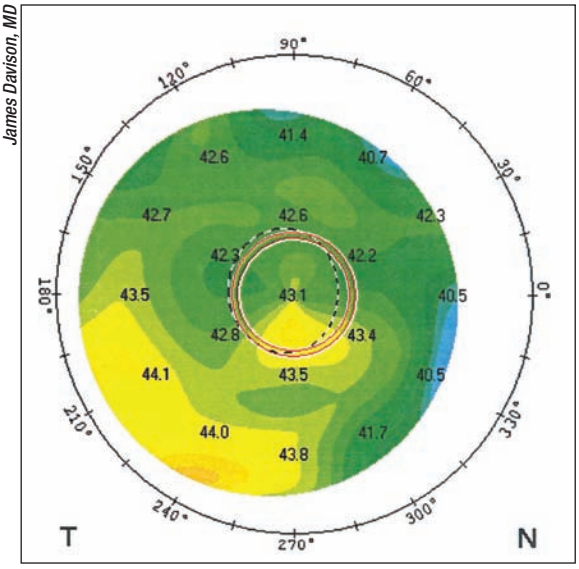
• ***Ocular surface.*** Since the tear film is the first thing incoming light hits on its way to the retina, surgeons say it better be in good shape if you want something as complex as a multifocal optical system to work properly. "Look at it this way," says George Beiko, MD, of Toronto, "if you have a television with a great picture tube but a dirty screen, you're not going to get a good image. You have to get everything working properly.

"Dry eye will impact all lenses," Dr. Beiko continues. "Even a monofocal IOL will be impacted. You can have a perfect surgery but the vision will still not be good because of dry eye or lid issues. Recently, I had a monofocal IOL patient whose vision wasn't good because of chronic blepharitis associated with acne rosacea. Last month I put him on some doxycycline, and when I saw him this month he said he noticed improvement. It will take three months for him to get the full effect. In a multifocal patient, fairly bad blepharitis would be a red flag, and is a common problem in the elderly, whether it's seborrheic blepharitis or blepharitis associated with acne rosa-

This article has no commercial sponsorship.

cea or Demodex mites. These conditions tend to lead to corneal surface disease and need to be treated fairly aggressively. For blepharitis, my first-line treatment is lid hygiene, from which I'll progress to ointments such as a combination steroid/antibiotic or a mild antibiotic like erythromycin on the lid margin. If that approach doesn't treat it effectively, or if someone has fairly severe acne rosacea, I'll go to an oral medication such as doxycycline."

Beverly Hills, Calif., surgeon Kerry Assil says that, even though dry eye is something that needs to be addressed, you'll know early on whether the person is a candidate for a multifocal or not. "Certainly, dry eye should be addressed in advance," he says. "However, if someone in the cataract age group has dry-eye disease, it will usually either be mild, which you can treat, or severe. So it isn't often a dilemma: If the dry eye is severe they wouldn't be a good candidate for a multifocal IOL."



James Davison, MD

This patient turned out not to be an ideal candidate for a multifocal lens because of substantially asymmetric keratometric astigmatism as represented by total corneal refractive power measured by the Pentacam. Total power at 3 mm was 42.4 D at 5.5 degrees (K1) and 43.5 at 95.5 degrees (K2).

Dr. Davison, who describes himself as conservative when it comes to selecting candidates for multifocal IOLs, says also to be wary of patients with lower-lid ptosis or retraction that's causing ocular surface problems.

• ***Corneal health and shape.*** Some corneal irregularities can be dealt with ahead of time, but some are deal breakers, doctors say.

"Anterior basement membrane dystrophy needs to be discussed with the patient," says Dr. Davison. "The patient may have variable vision throughout the day that he may not even be aware of as a result of ABMD. From a surgical perspective, the vision changes the patient will undergo—especially from using the drops immediately after surgery that will exacerbate the visual effects of the ABMD—will make recovery more challenging. You can laser or scrape the ABMD, but the patient will still have it. Even patients with monofocal toric lenses who have ABMD and significant visual changes have been disappointed postoperatively because they just don't function like they'd like to. So, someone with obvious corneal dystrophy probably wouldn't be a good candidate. However, someone with subtle ABMD but not other ocular problems could probably have a multifocal as long as it was accompanied by a frank discussion that the results may not be perfect, and that he may need to wear some correction or perhaps have another procedure postop."

Dr. Assil also watches out for corneas with unusual measurements. "Neither the ReSTOR nor the Tecnis performs brilliantly in patients with steep central corneas," he says. "This is especially true if they've had a significant amount of hyperopic LASIK previously, whereby the central cornea steepening (relative to the midperipheral cornea) is accentuated. Elevation maps and topographic maps will usually alert the surgeon, though a good rule of thumb is that anyone who's had more than 1 to 1.5 D of previous hyperopic LASIK might be a suboptimal candidate for a multifocal IOL. By the same token, a patient who's had more than 3 or 4 D of myopic LASIK could be problematic, because very few of those treatments are so perfectly centered as to enable synergistic optics with a multifocal lens. Also, in post-RK eyes, we have to select patients sparingly for premium IOLs."

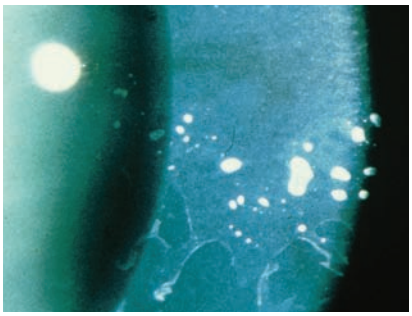
When it comes to corneal evaluation, surgeons note that you have to consider ahead of time how you're going to handle pre-existing astigmatism, and rule out patients with irregular cylinder. "Irregular astigmatism is a red flag," says Alexandria, La., surgeon R. Bruce Wallace. "However, patients with regular astigmatism of 0.75 D and lower could have a multifocal lens, though it depends on where the incision is and where the astigmatism is. If it's against-the-rule, then you're reducing some of that with a phaco incision. It's just the opposite in cases of with-the-rule astigmatism, where it will depend on where the astigmatism is located and how accurate your measurement is. For low levels like that, the topography may not even match the K readings that well."

Dr. Davison feels similarly, saying that you can't reliably deal with 0.5 D of astigmatism. "If someone has 0.75 D of astigmatism, I'll correct it with the femtosecond laser using 80 percent of the arc length suggested by the Donnenfeld nomogram, at 80 percent depth. For with-the-rule astigmatism I open the incisions because they're usually smaller and above and below the cataract incision. For against-the-rule, they're usually larger incisions

because they're paired with my cataract incision, and I won't open them because they're going to have a larger effect to begin with. I don't correct for 0.5 D because that's within the standard deviation of our measurement devices, so it's not something I can reliably measure and correct. However, multifocal patients with 0.5 D of astigmatism are usually happy, but it's still the great unknown. You don't know who is going to be happy and who's not. To gauge if someone will be happy, you've got to look at astigmatism in relation to all the other factors, such as their aberrations, the front and back surfaces of their cornea, their macula, the lens centration and their mental status."

Dr. Assil says that, if he is going to correct the astigmatism intraoperatively, the WaveTec VerifEye has become invaluable to him. "If the surgeon is trained on the proper use of the device, then the astigmatism may consistently be titrated down to the amount deemed appropriate," he says.

Dr. Beiko looks for nice, sharp mires on keratometry. "If they're sharp, it's likely the surface is good and there isn't anything negative going on," he says. "But if there are distorted mires, you have to use topography to take a good look to see if it's pellucid marginal degeneration or keratoconus. There are some elderly patients who have some degree of keratoconus that may not have been diagnosed. They may also have peripheral marginal disease, either guttering or thinning, that can also affect the quality of the light going through the cornea. If you see marginal disease or pellucid, it will be hard for the patient to be happy with the vision because it will distort the light coming through the cornea. I'll have a discussion with him about that, informing him that he's not the ideal candidate even though he might get some benefit from the multifocal lens. Sometimes, having had that discussion, the patient will want to go ahead with it and see what result he can get."



Surgeons say a multifocal lens is contraindicated in cases of frank epithelial basement membrane dystrophy.

Also be aware of any contact-lens-induced corneal warpage that can give false readings or mask other corneal problems. "Typically, we recommend patients stay out of soft contact lenses for a few weeks," says Dr. Beiko. "If they're in hard contacts, then stay out of them for a month or two. We perform an initial topography, then see them in a month to see if there's been any change. If there is a change, then we see them a month later, ultimately waiting until it's all stable."

• ***Specular microscopy.*** Gauging the overall health of the cornea can actually help pick out borderline cases. "If you perform specular microscopy and find that the patient has a low cell count relative to an age-matched group, or if the cells are irregularly shaped, that may indicate he's at risk for a corneal procedure later on, such as DSAEK or PK," advises Dr. Beiko. "You have to warn the patient that, if this occurs, the quality of vision will drop with a multifocal much more than it would with a monofocal IOL."

• ***Higher-order aberrations.*** Researchers and clinicians are beginning to get a sense that there are certain levels of higher-order aberrations that make it more challenging for a multifocal patient to tolerate his new lens. "Warren Hill, MD, has pointed out that corneal coma—positive or negative, vertical or horizontal—is indicative of increased visual symptoms and multifocal intolerance when it reaches a value of 0.32 µm or greater," says Dr. Beiko.[1] "Also, at the 2012 meeting of the American Society of Cataract and Refractive Surgery, Marc Michelson, MD, from Birmingham, Ala., presented a paper in which he found that patients with 0.12 µm of horizontal quatrefoil had trouble tolerating multifocality, while those with up to 0.07 µm could tolerate it. He also found that, in his patients who were unhappy with their multifocal lenses, the total RMS value of the third- and fourth-order aberrations was 0.23 or greater. Patients with third- and fourth-order aberrations totaling 0.18 µm or less were tolerant of multifocality. So, in patients who fall into these intolerant ranges, he basically won't implant multifocal lenses because they've got corneal issues that are generating these higher-order aberrations and making the vision poor."

• ***Retinal issues.*** A retinal issue that can arise in many patients is the presence of an epimacular membrane, and it may take work to suss out.

"To me, the way I look at it is this: You have to remember that these lenses are splitting up the light rays entering the eye so you're using less than 100 percent of the light for your reading material," says Robert Crotty, OD, an associate of Dr. Wallace's who participates in the preop evaluation of multifocal candidates. "So, if you're dealing with an epimacular membrane, even with a good retinal surgeon, the national average of improvement in vision is about 50 percent. Let's say the patient's vision improves to the 20/25 level. Though this is good vision, is a multifocal patient with reduced light transmission into the eye still going to have the quality of vision he needs at that level? Now, if it's only in one eye and the other eye is healthy, he may do well. We have a few patients who have multifocal implants in only one eye and they do OK. I think it's going to be a case-by-case process."

Recognize both.
Recommend AcrySof® IQ Toric IOL.

CONFIDENCE | THE ACRYSOF® ADVANTAGE

Recommend the AcrySof® IQ Toric IOL for your astigmatic cataract patients.

ACRYSOF® IQ TORIC ASTIGMATISM IOL

For important safety information, please see adjacent page.
 2/13 TOR13020JAD

Alcon®
a Novartis company

Though some surgeons are moving toward performing optical coherence tomography on all their prospective multifocal patients, Dr. Beiko says you can begin with a good posterior exam with either a 60- or 90-D lens and, if you have any suspicions, move on to an OCT. "Typically, when someone has an epimacular membrane and you take it out, the vision won't be perfect. I think this type of case would be on the borderline, and most surgeons would shy away from implanting a multifocal."

A substantial amount of macular degeneration would be a contraindication, but some surgeons say there are exceptions. "If it's a tiny amount of drusen, I think it would be OK," says Dr. Davison. "The same goes for a small amount of RPE pigment changes in an older person. But, if someone is 55 years old and he's starting to show those signs, I'm not sure that's the type of person I want to put a multifocal in, because if he lives to be 80 then sooner or later he'll likely suffer some macular dysfunction."

• ***Anticipate halo/glare problems.*** Surgeons note that some patients are more sensitive to qualitative problems than others. "What I say to cataract patients is that any IOL we put in their eyes, even a monofocal lens, has a risk of glare and halo, but that multifocal IOLs have a slightly higher risk," says Dr. Beiko. "I also inform them that it takes about six months to adapt to that change. So, the contract has to be in place that states if the patient is going to have a multifocal he's aware of this risk and will give it at least six months before giving up."

Intraoperative Factors

Small parts of the surgery itself can prove to make a big difference if they're not executed well, say surgeons.

• ***Centration.*** Dr. Wallace says there are aspects of the lenses themselves that can help you avoid a decentration that can decrease results. "What's nice about these multifocal IOLs compared to monofocals is that you can tell how well they're centered using their rings," he says. "I like to be 0.5 mm nasal rather than in the middle of the pupil, because I think that's where the sweet spot is for the quality of vision." This sentiment demonstrates what Dr. Davison believes: "I think you center these lenses where they look good to you, which is maybe the center of the pupil, the limbus or maybe both," he says. "I'm not sure I believe everything I hear about factoring in angle kappa when centering these lenses. Some surgeons say at the end of surgery you should nudge the lens over and it will be perfect, but I don't believe in nudging it. These lenses go where they want to go, though I think you can influence their position by rotating them to an optimal location within the capsular bag so they appear to be centered better to you. Empirically for me, that position turns out to involve orienting the haptics supero-temporal to infero-nasal. I don't have any study that shows this orientation is superior, but that usually gives me the best result."

• ***Avoid leaks.*** Surgeons say that you could pick the best patient and the ideal lens but still falter at the finish line. "Make sure the entry site is well-sealed at the close of surgery," says Dr. Assil. "This isn't just for the obvious reasons of avoiding inflammation and infection, but also to avoid a shift in the IOL's position due to IOP decrease from the wound leak. This is even more important with toric IOLs."

Dr. Davison says that, if you pay attention to the small factors as well as the large, and select patients carefully, working with multifocal lenses can be rewarding. "There's no one more happy than someone with a multifocal lens who sees well—it's wonderful to see," he says. "However, there's no one more unhappy than someone who has expectations of multifocality and good functional vision but doesn't get it—then it's a disappointing and regrettable experience for everyone." REVIEW

1. Warren Hill, personal communication

Trade Up To Keeler

Trade-in your old Kowa hand-held slit lamp & get $600 towards Keeler's Advanced PSL Classic!

Powerful & Portable!

- Precision machined aluminum chassis
- Advanced optics, x10 & x16 magnification
- Controllable illumination from maximum to zero
- Most Apertures and filters along with 1.mm square light patch for assessing a/c flare

Trade-in & Special Bonus
FREE iPhone 4 Adapter and Carrying Case.
Offer expires March 31, 2014.

Buy Online!
keelerusa.com

Keeler
OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

Refractive Surprises After Cataract Surgery

Michelle Stephenson, Contributing Editor

The best treatment depends on the amount of residual error.

When it comes to refractive surprises after cataract surgery, an ounce of prevention is worth a pound of cure, and surprises can be anticipated in certain patients.

"We should anticipate refractive surprises when an eye is extremely myopic or extremely hyperopic, so in very large or very small eyes," says Kevin M. Miller, MD, a professor of clinical ophthalmology at the Jules Stein Eye Institute at UCLA. "With conventional lens power calculations, even when the appropriate formula is used for extreme myopes and extreme hyperopes, patients can end up hyperopic. We have to adjust our calculations for extreme cases, targeting for a bit of residual myopia. For example, if the SRK/T formula predicts a negative power IOL in axial myopia, I will usually choose the IOL power that targets for -1.5 D of postoperative myopia, expecting to hit emmetropia by doing so. If the Hoffer Q formula predicts a 38 D IOL in axial hyperopia, I will often choose a 39 or 40 D IOL instead, expecting to achieve emmetropia by doing so."

Dr. Miller also anticipates refractive surprises in patients who have previously undergone RK, PRK or LASIK. Additionally, there can be surprises in post-penetrating keratoplasty patients and in cases where the anterior segment of the eye is disproportionately sized compared to the overall length of the eye.

However, when refractive surprises occur with no warning after routine cataract surgery, it is important to stay calm. Dr. Miller says the best course of action is to remain the patient's advocate and not to let the situation become adversarial.

Colorado Springs-based surgeon Steve Dewey, MD, notes that preoperative IOL counseling can help prepare patients for surprises. "I let the patient know that while this looks like we're playing darts, it's really horseshoes," he says. "We're trying to get patients as close as possible to their goal, but we won't know exactly how close we're going to be until after the surgery. I typically do the nondominant eye first if we are doing both eyes. I tell patients that I can adjust the implant power for the dominant eye and make their vision closer to our target. It is rare to find someone who doesn't tolerate 1 D of myopic anisometropia, but it happens. Then, you have to discuss with the patient how she wants to proceed."

Determining What Went Wrong

Once you realize that the patient's

This article has no commercial sponsorship.

vision is not what you expected, it is important to re-check and re-perform all of your calculations. "We need to go back and Monday night quarterback what happened to this eye," says Lisa Arbisser, MD, adjunct associate professor at the University of Utah's Moran Eye Center.

The first step is to make sure that the right patient has the right lens. "I had one instance where two patients' lenses were switched," says Richard S. Hoffman, MD, who is a clinical associate professor of ophthalmology at the Casey Eye Institute at Oregon Health & Science University. He is also in private practice at Drs. Fine, Hoffman & Sims. "Then, I make sure that the right data were put in the Holladay, and I make sure that the axial length and K readings were put in correctly. Little surprises are somewhat common, but when you get a huge 2 D to 3 D surprise, you want to know that the right patient got the right lens and that the data were put in correctly."

The next step is to look at the type of lens that was implanted and determine whether there is something about the eye that could cause the problem. "For instance, if the Crystalens is implanted upside down, you get a myopic shift," says Dr. Hoffman. "There are safeguards on that lens to make sure that it is placed right side up, but accidents can still happen. Additionally, a capsular block can cause a forward movement of the lens and a myopic shift. That is very easily dealt with using a YAG capsulotomy."

Dr. Arbisser notes that the refraction may not be stable immediately after surgery in some patients. "In a patient who has had RK, the refraction may not be stable for one to three months," she says. "Patients with a one-piece acrylic lens are typically stable on day one. But, after implanting a Crystalens, the refraction can continue to change over two weeks or more. With a Crystalens, I would not consider correcting a refractive error for two weeks."

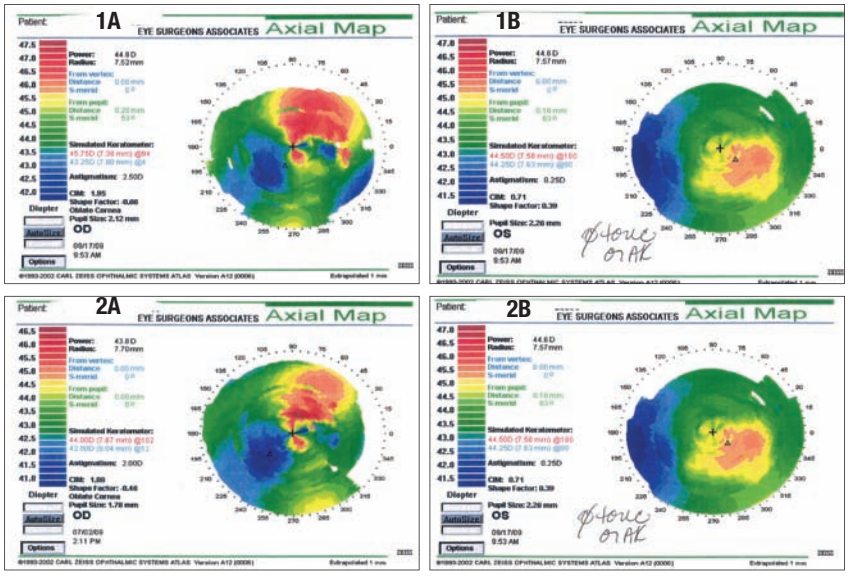


Figure 1. Preoperative and postoperative superficial keratectomy patient topography going from 2 D of cylinder to none in one eye and 4.5 D to almost none in the other.

In some cases, the residual refractive error may not be in the eye that was operated on. "Sometimes, the problem is that the eyes just don't work together after you have operated on one. You have to consider the binocular situation and not just the monocular situation," Dr. Miller says.

If the eye that just underwent cataract surgery has a bad refractive outcome, the options are limited to glasses or contact lenses, corneal refractive surgery, or a lens exchange or piggyback lens. "We can always fix refractive errors with glasses and contact lenses, so we have to be sure that that isn't the patient's choice because anything we do will carry some risk associated with it, and there will be a cost to someone, depending on how you structure your costs," Dr. Arbisser says.

"If it is pure mixed astigmatism, we can perform peripheral corneal relaxing incisions," says Dr. Miller. "For small amounts of spherical or spherocylindrical error, I use PRK or LASIK. For larger amounts, I would choose a lens exchange or piggyback IOL."

Corneal Refractive Surgery

For small amounts of residual error or to finesse the results, PRK or LASIK may be the best choice. "There is more finesse with PRK and LASIK than there is with lens exchange or piggybacking," Dr. Miller says. "With the latter options, the finesse is 0.4 to 0.5 D at best, and you can get down to 0.1 to 0.2 D with PRK and LASIK. In terms of optical outcomes, PRK and LASIK are the same. However, in the older patients who tend to fill the cataract ranks, I generally prefer PRK over LASIK because there are fewer dry-eye problems. For younger patients, I usually offer a LASIK enhancement."

He notes that, if you are going to do a touch-up procedure, you have to make sure to wait long enough to achieve total refractive stability and an incision that's very tight. "I would never consider doing LASIK sooner than one month after surgery, and, practically speaking, I almost never do PRK or LASIK until at least three months has elapsed," says Dr. Miller.

PCRIs are a good choice for patients with up to 2.5 D of mixed astig-

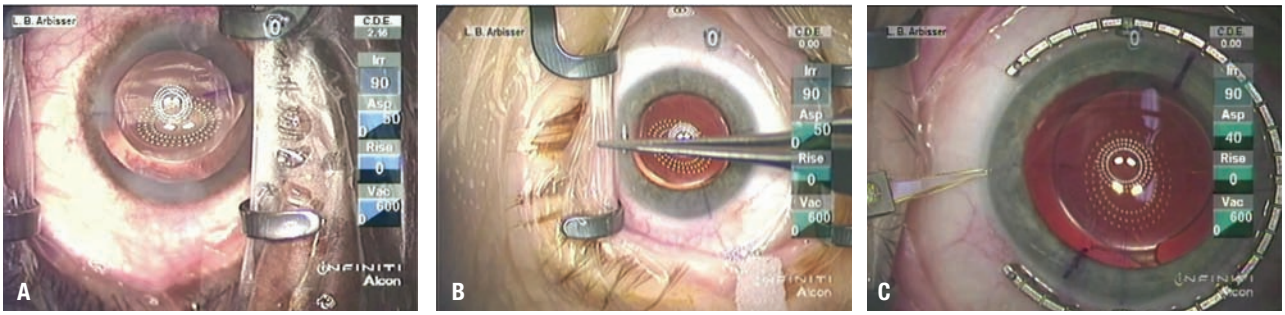


Figure2. Mastel keratoscopy showing toric on-axis (a), off-axis (b) and with the forceps aligned on one axis highlighting that the lens needs rotation (c).

matism, as long as the spherical equivalent refractive error is 0.

Lens Exchange

According to Dr. Miller, lens exchange is reserved for patients who have one of two problems: Either they have a really significant refractive error or there is a problem with the lens itself. "I don't typically exchange lenses for small refractive errors," he says. "Sometimes, the new lens will have a different vertex or the actual powers of the old and new IOLs will be slightly different than the powers listed on the boxes. Unfortunately, the mentality of many patients is that if the problem is with the lens, then we should swap out the lens. In this situation, you have to explain that you can probably achieve a better refractive outcome by not swapping out the lens, but by performing keratorefractive surgery instead. If a patient has a multifocal in the eye and he or she has poor-quality vision or waxy vision, then it makes sense to do a lens exchange. In certain cases, the diffractive surface of the optic may have been damaged. If you give patients adequate time to recover their distance and near vision, and they don't, it is probably a deformed diffractive optic. In this situation, I would go to a lens exchange before I would perform a keratorefractive procedure. That's my general approach. However, some patients just want the lens out. I have done lens exchanges for less than 1 D of refractive error because a patient wanted a better refractive result but did not want corneal surgery."

He notes that he always wants to have the option of a lens exchange, so he aggressively polishes the lens epithelial cells off the anterior lens capsule. "I try to get every last cell out; I never actually achieve that, but I try. As such, I can take out a lens five or six years later. It's almost like re-opening a LASIK flap. I generally wait three months or so before I do touchups, unless it is a toric lens that is malpositioned," he says.

He does not believe in waiting for neuroadaptation in premium lens patients. "I think we are dealing with a deformed lens in most cases," he says. "Sometimes, you have to wait for the lens to regain its shape once it is placed in the eye. If you wait long enough on a multifocal patient who is complaining of waxy vision, he or she often will slowly get better. People call that neuroadaptation, but what has really happened is that the lens has slowly regained its factory-manufactured shape. With waxy vision, I wait to see if it gets better because if it doesn't, I'm not going to do PRK or LASIK. Instead, I'm going to take that lens out."

Dr. Arbisser agrees that subtle refractive errors are not well-addressed with lens exchanges. "If we have a larger refraction problem, then piggybacking can be an option," she says. "If we are going to piggyback a lens, my choice is a Staar AQ series because it is 13.5 mm from haptic to haptic, so it fits every sulcus. It has a nice smooth anterior edge and a little bigger optic. For all those reasons, it is really made as a sulcus lens, and it is the best choice for a planned piggyback lens. It comes in +5 to -5."

Piggybacking a lens is the easiest surgery, according to Dr. Arbisser, but it has the largest long-term potential risk, in that, despite using the best sulcus lens, it is possible to get pigmentary dispersion. Additionally, there is the cost of the extra lens.

Dr. Hoffman notes that piggyback lenses are usually covered by insurance, while corneal refractive surgery isn't. "The piggyback lenses that we have in the United States won't treat astigmatism, but corneal refractive surgery does treat the astigmatism, so my preferred method is to do the corneal refractive surgery," he says. "However, patients have to pay extra to have that done. When I'm doing premium lenses, I make patients aware of that additional cost upfront. Some people just do it as an all-inclusive fee, and some people do it a la carte, which is my preferred method. Placement of a piggyback lens is a little bit more straightforward."

Rotating a Toric Lens

For toric lenses, rotating the lens may fix the issue. "We have an astigmatic error calculator online," Dr.

Arbisser says. "We put in our preop and postop measurements, and the calculator tells us what we have to do to fix it, which is usually rotating the lens. If the lens was good on day one and then rotates, that's another story. If it went in wrong, and you can see that you can rotate it back to where it ought to be, then I think that's the thing to do."

If the first eye has a toric that is a little bit off, the surgeon can compensate when she does the second eye. "I had a patient who was fine on day one but then rotated and had some residual astigmatism," Dr. Arbisser says. "This was the eye that had the most astigmatism. He decided to save the money on the toric lens in the other eye, and we left both eyes with a little bit of residual astigmatism. He was very happy with the result."

According to Dr. Dewey, correcting these surprises depends on the comfort of the surgeon, which IOL was used, and how long it has been since the lens was implanted. "If it's as simple as a malrotated toric IOL, simply rotate it into place at an early stage," he says. "These can be rotated months later, but the lens is going to want to go back into its little fibrosed space in the capsule, making precision a bit more challenging. If it is a perfectly rotated toric, or if it's a simple myopic or hyperopic error several months or years later, I think a piggyback with the Staar AQ5010V makes the most sense."

Dr. Miller adds, "The original incision should be reopened whenever possible and the malpositioned toric IOL should be aligned with the postoperative axis of corneal astigmatism, not the axis originally targeted by the toric calculator. These two axes will likely be slightly different. The goal is to have the toric optic aligned with the axis of steepest postoperative corneal cylinder."

The Future

According to Dr. Arbisser, in the future, surgeons will have technology that theoretically will be able to touch up the refraction by changing the lens itself postoperatively, such as the Calhoun lens in FDA trials, for which Dr. Miller is an investigator. "The most exciting technology is using a femtosecond laser in a proprietary method that is being worked on at Rochester University to actually correct the prescription without wound healing issues by changing the refractive index of the cornea as well as any implant. It could be that, in the far future, we won't need contacts or glasses or ever get a wrong implant," she says. REVIEW

Surgeons Choose the Premium Channel

Walter Bethke, Managing Editor

Good results in select patients are making premium IOLs more appealing to surgeons.

Presbyopic intraocular lenses appear to be making inroads in cataract surgeons' practices, with 72 percent of the ophthalmologists surveyed in our latest e-survey saying they use them. The counterpart to presbyopic lenses in the premium channel—toric IOLs—are even more popular, with 85 percent of the survey's surgeons implanting them. The surgeons also say they prize asphericity/neutral asphericity and a toric design when it comes to the construction of an IOL, but they are less enthusiastic about blue-light blocking.

These are just some of the results from this month's e-survey on IOLs. The e-mail survey was opened by 1,315 of the 10,000 subscribers to *Review*'s electronic mail service (13 percent open rate) and, of those, 82 surgeons (6 percent) responded.

Presbyopic Lenses

Breaking down the popular option of presbyopic lenses, 46 percent use the AcrySof aspheric ReSTOR +3 D, 41 percent implant the Tecnis multifocal lens and 29 percent implant the Crystalens (some surgeons implant more than one of those lenses). Though they're using the lenses, the surgeons aren't implanting them with great frequency: On average, they implant an average of five ReSTOR lenses, eight Tecnis lenses and/or three Crystalens IOLs per month. The aver-

Surgeons Rank Features of IOLs

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

age charge for these premium IOLs on the survey is $1,884 for the ReSTOR, $2,015 for the Tecnis and $2,250 for the Crystalens.

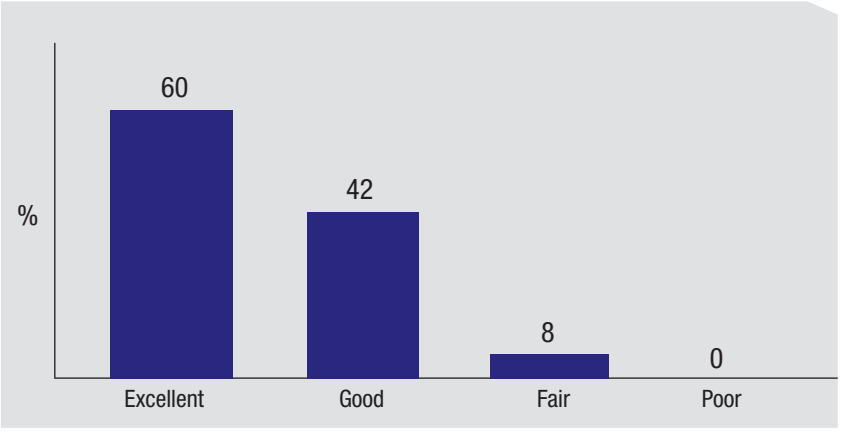
Surgeons appear to be satisfied with presbyopic lenses, with 31 percent saying they're very satisfied, 36 percent identifying themselves as satisfied, 29 percent saying they're somewhat satisfied and only 4 percent saying they're unsatisfied. "Centration of multifocal lenses is key," says Anil Shivaram, MD, of Claremont, Calif. "Also, do your due diligence to make sure the patient is a candidate in the first place. The current multifocals out there do have a gap in intermediate compared to near/distance. I certainly look forward to other IOL technologies like the FineVision lens. Crystalens is not always predictable and success seems predicated on mini-monovision at times. A truly accommodative lens will be a reality at some point, but until we fix the effective lens position problem ... it still remains elusive."

Dayton, Ohio, surgeon Kurt Andreason feels similarly, saying, "A multifocal lens causes halos and cuts the light from both near and distance, and has limited intermediate vision. A truly accommodating platform would be better of course—but good luck." James Davies, MD, of Carlsbad, Calif., says he implants the Crystalens the most of all the presbyopic lenses, but thinks it could be improved with "greater accommodation." It does have some strong points for him, though. "The predictability of the refraction is very good," he says. "Patient satisfaction is also very high, but good results are extremely technique-dependent. It's also critical that patients use NSAID and steroid drops longer than with a monofocal or multifocal IOL."

Toric IOLs

Toric IOLs are a favorite premium lens for survey respondents, with 85 percent saying they implant them. Fifty-eight percent of the toric lens users rate their performance as excellent and a third describe it as good. Only 8 percent would rate it as fair.

Surgeons Rate Toric IOL Performance



"The toric lens is essentially a slam dunk for most patients," says Dr. Shivaram. "However, the high-myope, floppy bag patients are still a challenge and I wish that the IOLs could be sized to take those diopter ranges into account." Moultrie, Ga., ophthalmologist Terry Croyle also feels that patients respond to toric lenses. "These lenses really give the cataract patient the wow factor that can make the difference between a so-so subjective perception of the value of the surgery we perform and the uber-happy patient who can't say enough good things about the surgery."

R. Wayne Bowman, MD, of the University of Texas Southwestern Medical center says toric lenses are great, but you have to make sure you implant them properly. "They work as advertised," he says. "The most difficult part is actually determining the amount and axis of total corneal astigmatism that needs to be corrected."

One surgeon, who elected to be anonymous, says he uses the AcrySof toric currently, but is open to other options down the road. "I'm looking forward to implanting the Trulign," he says. "However, I require a perfect corneal surface, perfect zonule integrity, perfect pupil function and very symmetrical central topography to offer a toric IOL. I also must have a patient with great patience to go through the wait to support his ocular surface properly."

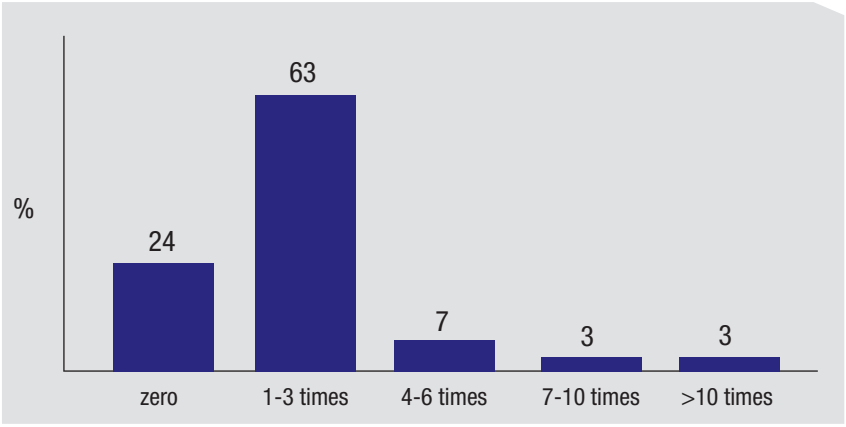
Some surgeons say toric lenses aren't perfect, however. A surgeon from California says, "I'm using them less, now that I can do femtosecond laser arcuate incisions and get the other advantages in addition to the reduction of cylinder." Another surgeon says he occasionally has "some difficulty with lens rotation in long eyes," while a surgeon from North Carolina opines, "With toric lenses, there are many variables that can cause inconsistent results."

Materials and Features

Surgeons on the survey also had opinions on the best IOL material, as well as what they like about the implants that they use for the majority of their cases.

When it comes to the monofocal lens surgeons use for most of their cases, 52 percent say they use the Alcon IQ Aspheric, 29 percent use the AMO Tecnis, 8 percent use B + L's SofPort AO aspheric lens and 6 percent use the Lenstec Softec HD. The Rayner C-flex, Staar Nanoflex and B + L enVista were each chosen by 2 percent of the

Surgeons' Annual Frequency of Suturing an IOL



survey respondents.

"I use the Alcon IQ and the Softec HD Oval," says Richard Phinney, MD, of Rock Island, N.Y. "With the IQ, I like the predictability of insertion, good centration. With the HDO, I like its depth of focus and the fact that it's great for blended vision." A Wisconsin surgeon says the IQ has several pluses as well as some drawbacks. "I like the fact that it is uniplanar, the AcrySof material keeps it adherent to the capsular bag and in position, the haptics are sized for bag fixation, the edge design minimizes posterior capsule opacification, it is aspheric and it has a yellow tint that I believe helps decrease the risk of ARMD," he says. "The design also makes it easy to insert and manipulate directly into the bag. I don't like the fact that 0.5-D steps are not offered at the lower and higher range of powers and that the range of powers is limited at both the high and low ends."

Bruce Cohen, MD, of St. Louis, is in the Tecnis camp. "It's a beautiful lens," he says. "It's got clear, aspheric optics without blue blockers or glistenings, is easily inserted through a 2.5-mm incision, and has no rapid capsule opacity." Ellicott City, Md., surgeon Marjorie Warden also likes the Tecnis, saying, "It's easy to implant, is one-piece acrylic and doesn't have glistenings." Dr. Shivaram likes the enVista lens. "It's cryolathed and aspherically neutral," he says. "It's also the only lens to be shown as glistening-free. It has good centration and a low rate of PCO."

Material-wise, 80 percent of the surgeons think acrylic is best, 8 percent prefer silicone, 5 percent like PMMA and 3 percent each go with collamer or hydrogel.

A surgeon in the acrylic group sums up his affinity for the material: "First, its slow folding and unfolding properties make IOL loading into the injection cartridge easier and IOL insertion into the eye safer—there's no rapid release of energy as the IOL emerges from the injector," he says. "Second, its material properties—tackiness—help keep the IOL centered and positioned in the bag (and on-axis, if using a toric IOL). Also, there's no late IOL decentration with acrylic IOLs as is sometimes seen with three-piece silicone." For his part, though, John Doane, MD, of Independence, Mo., likes silicone. "I like its ease of use," he says. "Silicone also has essentially zero internal reflectivity, while acrylic has the highest internal reflectivity."

Suturing and Explants

Surgeons say that, occasionally, an IOL will shift position and require some sort of intervention to re-align it. Sixty-three percent say that they have to go back in and suture one to three lenses per year, 7 percent need to suture re-fixate four to six lenses, 3 percent do it for seven to 10 lenses and another 3 percent have to suture more than 10 lenses each year. Twenty-four percent say they don't suture any lenses during the year, either because of no complications or because they refer them to another surgeon.

Reasons for suturing include: no capsular support; angle compromise; late in-the-bag dislocation in cases of pseudoexfoliation; and cases of ocular trauma. Las Vegas surgeon Robert Taylor III says an anterior chamber lens can be an option, also. "Loss of capsular support from pseudoexfoliation or zonular dehiscence is the common reason for having to suture a lens," he says. "I most commonly employ iris or scleral suture fixation. There is also still a role for an appropriately sized and placed anterior chamber IOL in select patients in whom there is good anterior chamber depth, no glaucoma and a healthy corneal endothelium. In these patients, there is probably less intraoperative trauma and equally good visual outcomes."

Surgeons also reported the reasons they had to explant lenses and replace them with new ones in the past year. The reasons given on the survey included:

- glare and halo;
- incorrect lens power;
- waxy vision;
- pseudoexfoliation;
- uveitis/glaucoma/hyphema syndrome; and
- pigment on the lens.

"Improper power of the IOL is common," says Dr. Taylor. "This is most commonly seen after cataract surgery in a previous refractive surgical patient." One surgeon though, says he thinks a preop DIY approach lets you avoid explantations. "I've never had to explant a lens," he says. "I choose the correct lens preop and don't have my staff perform the exams." REVIEW

Invest In Your Practice And Get A Guaranteed Positive Return.

Lombart's CS-4 Package Offers Quality, Style & Value.

Ask about optional Slit Lamp & Chart Projector configurations.

$13,595

Or lease for $269/mo. for 60 months *

Package includes:

- The Lombart CS-4 Chair & Stand
- Topcon VT-10 Refractor
- Topcon SL-2G Slit Lamp
- Reichert LongLife Chart Projector with mount, slide & screen
- Upgrade to the Lombart CVSi21 for only $2000 more or to the CVS-PC for only $1500 more — Additional upgrades & configurations available.

(1-800-566-2278)

Call 1-800-Lombart

Or Your Local Lombart Representative.

Corporate Office - 5358 Robin Hood Road, Norfolk, VA 23513-2430
757-853-8888 | FAX 757-855-1232 | 800-566-2278 | 800-446-8092
www.lombartinstrument.com

ATLANTA•BALTIMORE/WASHINGTON D.C.•BOSTON•BOYNTON BEACH/MIAMI•BRADENTON•CHARLOTTE
CHICAGO•CINCINNATI•DALLAS•DENVER•DETROIT•GREENSBORO•HOUSTON•KANSAS CITY•KNOXVILLE•LOS ANGELES
MILWAUKEE•MINNEAPOLIS•NEW JERSEY/NEW YORK•NORFOLK•PORTLAND•SACRAMENTO•SAN DIEGO•SAN FRANCISCO

***Lease rate subject to credit approval, 1st payment is paid for by leasing company at signing with 59 remaining rental payments of $269 and a $1.00 purchase option. Taxes, freight and installation additional. Hand Instruments optional. Quantities limited. Subject to change without notice.**


Managing Submacular Hemorrhage

This potentially visually devastating condition is most commonly associated with choroidal neovascularization due to AMD.

Sarah Driscoll, MD, and Sunir J. Garg, MD, Philadelphia

Submacular hemorrhage results from choroidal and retinal vessel abnormalities. Submacular hemorrhage frequently results from a choroidal neovascular membrane secondary to age-related macular degeneration. Other conditions associated with CNVM, including myopia, trauma, ocular histoplasmosis and angioid streaks, can also lead to submacular hemorrhage.[1-3] A small, thin SMH can often be observed *(See Figure 1)*, while massive submacular hemorrhages often have a poor prognosis regardless of intervention.[1] Thick, medium-sized subretinal hemorrhages that extend under the macula and obscure the underlying retinal pigment epithelium can also cause significant vision loss; however, they are often amenable to treatment.[1]

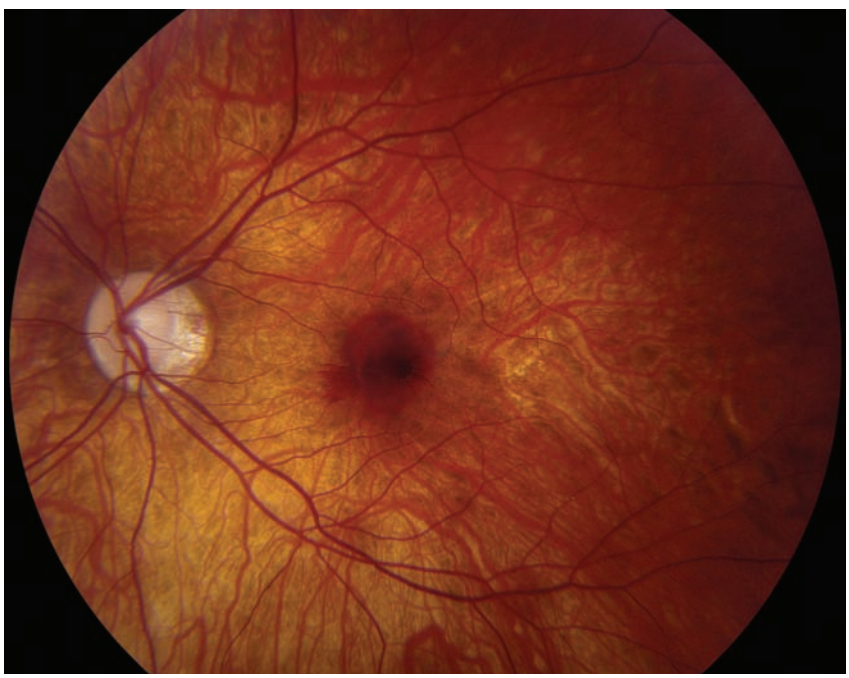


Figure 1. A small subfoveal hemorrhage due to myopia that would be appropriate for observation.

Mechanisms

Subretinal hemorrhage damages tissue through a variety of mechanisms: The presence of iron, hemosiderin and fibrin in the blood has toxic effects on the overlying photoreceptors; clot retraction can sheer and damage the photoreceptors; and finally, physical separation of the photoreceptors from the RPE causes both to atrophy and can result in disciform scar formation. As the mechanisms of damage are time-dependent, early intervention is generally better.

Patients with submacular hemorrhage experience progressive visual decline. A retrospective review looked at 41 eyes with AMD-related SMH that were followed without treatment. At three years, patients

This article has no commercial sponsorship.

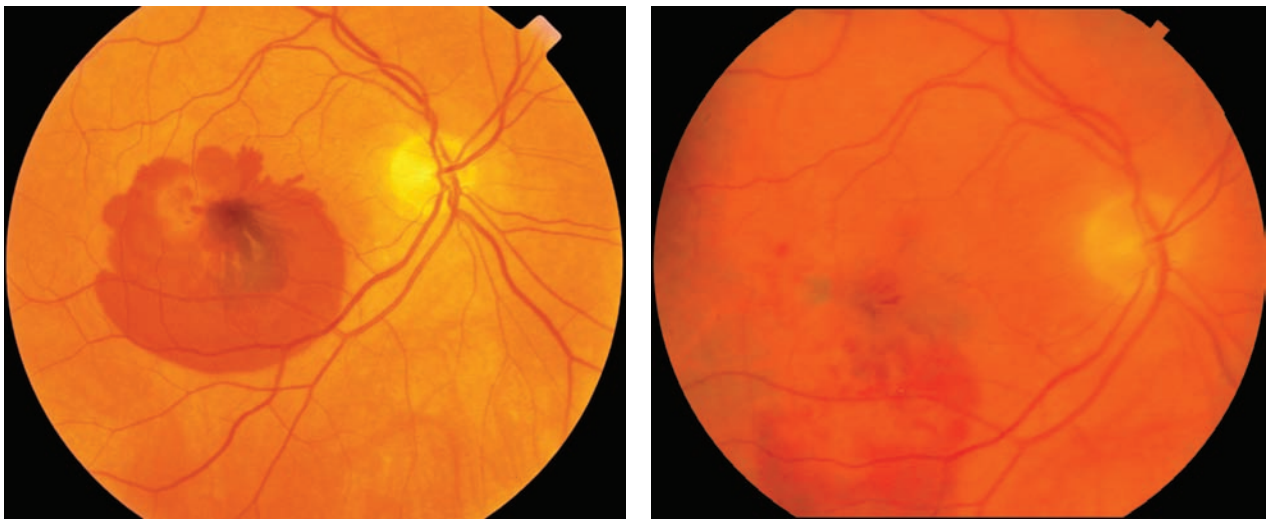


Figure 2. A) This patient had 20/400 vision with a thick submacular hemorrhage. B) One month after surgery the vision improved to 20/60 with excellent displacement of the hemorrhage.

lost a mean of 3.5 lines and 44 percent suffered a six-line loss of vision.[3] Due to the often severe, progressive vision loss, a number of treatments have been tried. Photodynamic therapy offers the benefit of a minimally invasive, in-office procedure, but has shown uninspiring results. Patients treated with PDT for AMD-related submacular hemorrhage followed for 12 months had no significant difference between initial and final visual acuities. PDT may favorably alter the course of natural history by preventing further vision loss.[4] However, visual acuity at presentation with SMH is so poor that stability alone is not an exciting endpoint.

Treatment Options

There are a variety of treatments targeted at the removal or displacement of the hemorrhage. Some techniques are office-based, while others are performed in the operating room. Pneumatic displacement of SMH (with and without tissue plasminogen activator [t-PA]) is an office-based procedure first described by Wilson J. Heriot, MD, in 1996 and has shown some success in subsequent small case series.[5-8] This technique attempts to physically displace the SMH out of the fovea using expansile gas. The procedure is performed under topical anesthesia and involves an intravitreal injection of 0.3 to 0.4 ml of either shorter-acting sulfur hexafluoride (SF6) or longer-acting perfluoropropane (C3F8) followed by face-down head positioning for one to three days.[1,9,10] Complications of pneumatic displacement include vitreous hemorrhage; endophthalmitis; retinal detachment; and recurrent hemorrhage.[1] Case series have shown the ideal candidates for pneumatic displacement are those with thick SMH less than three weeks old involving or inferior to the fovea. Although SMH predominately superior to the fovea can benefit from treatment, this type of hemorrhage may be displaced into the subfoveal space resulting in worse vision.[10]

Dr. Heriot's initial description of this procedure included intravitreal t-PA injection to facilitate clot liquefaction and pneumatic displacement. *(Heriot WJ. Intravitreal gas and RT-PA. An out-patient procedure for submacular hemorrhage. Paper presented at: Vail Vitrectomy Meeting. 1996 Mar 10-15; Vail, Colo.)* Many subsequent small case series demonstrate that the addition of 0.1 to 0.2 mL of intravitreal t-PA (either 25 µg or 50 µg/mL) can be beneficial, especially for AMD-related SMH.[5-7,11] Because this technique includes the additional volume of t-PA, an aqueous tap to maintain physiologic intraocular pressure is usually required. To allow time for the t-PA to diffuse through the vitreous and lyse the clot, prone head positioning should start six hours after injection.

The additive role of t-PA has been debated. One study did not find a beneficial or harmful effect with addition of t-PA,[12] while other reports suggest that t-PA can cause retinal toxicity including electroretinogram changes and RPE alterations.[13,14] Moreover, some investigators question whether intravitreal t-PA crosses the subretinal space. Motohiro Kamei, MD, and colleagues injected fluorescein-labeled t-PA into rabbit eyes and did not find any histopathologic evidence that t-PA can diffuse across an intact retina.[15] However, other investigators disagree with that assertion.[16] Some physicians feel pneumatic monotherapy is more appropriate for those patients with non-AMD-associated SMH treated

CME

Save the Date!
January 23-25, 2014
Grand Summit Resort
Park City, Utah

REACHING NEW PEAKS IN Ophthalmic Surgery

Course Director
Alan S. Crandall, M.D.
Salt Lake City, Utah

Co-Director
Douglas D. Koch, M.D.
Houston, Texas

Co-Director
Stephen Lane, M.D.
St. Paul, Minnesota

Hotel Information:

Grand Summit Resort
4000 Canyons Resort Dr.
Park City, Utah 84098
(888) 226-9667

Discounted room rates are limited and based on availability, so please book early! Identify yourself as a participant of the **Reaching New Peaks in Ophthalmic Surgery Symposium**.

Sponsored by

PIM Postgraduate Institute for Medicine

Endorsed by

REVIEW® of Ophthalmology

Partially supported by an independent medical educational grant from

Alcon®

BAUSCH + LOMB

MST

REGISTER NOW!

For more information and to register:

www.pimed.com/ReachingNewPeaks2014

Phone: 866-627-0714 or Email: CMEMeetingLogistics@pimed.com
CMERegistration@pimed.com

Accreditation Statement: The Postgraduate Institute for Medicine (PIM) is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: PIM designates this live activity for 15.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

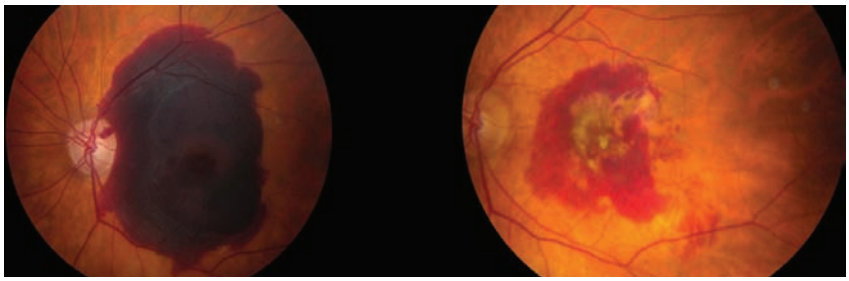


Figure 3. Left: preoperative image of submacular hemorrhage from choroidal neovascularization secondary to age-related macular degeneration. Right: postoperative image after pars plana vitrectomy with subretinal tissue plasminogen activator and pneumatic displacement. There was incomplete displacement of the hemorrhage.

within one week of presentation.[8,14] However, most practitioners feel that t-PA augments pneumatic displacement and that diffusion is facilitated through presumed microscopic retinal breaks in eyes with SMH, especially those with concurrent intraretinal or vitreous hemorrhage,[5-7,15] and concentrations ≤ 25 µg show a favorable efficacy and safety profile.[5,10,14,17]

Over the past decade, anti-VEGF agents have changed the AMD treatment paradigm. Patients with thick SMH were excluded from the trials that led to Food and Drug Administration approval, however, three case series have looked at the treatment of SMH secondary to AMD with anti-VEGF alone.[18-20] In each study, the investigators followed patients with AMD and SMH monthly and administered intravitreal injections of either bevacizumab or ranibizumab alone with favorable results. The authors concluded that intravitreal anti-VEGF monotherapy is superior to natural progression and is a reasonable alternative for poor surgical candidates, patients intolerant to prone head positioning or patients with subretinal hemorrhage that may be displaced directly into the fovea.

Surgical Approaches

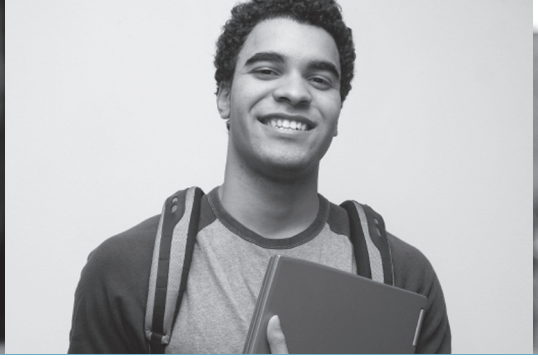
Various surgical attempts to manage this difficult condition have been tried, including direct clot evacuation. Following pars plana vitrectomy, the clot was directly evacuated through one or more retinotomies either with or without adjuvant subretinal t-PA injection. In a few of the small case series some patients did show initial visual improvement; however, many reported significant postoperative complications, including retinal detachment, recurrent hemorrhage and subretinal fibrosis.[21-24] The Submacular Surgery Trial offered a more objective evaluation as a randomized clinical trial that compared direct evacuation of the CNV/hemorrhage complex to observation and found evacuation did not stabilize or improve vision and carried a high risk of rhegmatogenous detachment.[25] For these reasons this technique has largely been abandoned.

Christopher Haupert, MD, and colleagues described a hybrid surgical approach that combined the concepts of pneumatic displacement with subretinal t-PA administration in a manner that required minimal manipulation of the retina and RPE *(See Figures 2 and 3)*.[26] They described 11 cases that underwent PPV and subretinal injection of 25 to 50 µg of t-PA through a microcannula *(See Figure 4)* followed immediately by fluid-air or fluid-gas (SF6) exchange with postoperative prone head positioning. There was no attempt to directly evacuate the clot. The results of their series were comparable to other more invasive series and demonstrated modest visual gains in a number of patients.

Sébastien Oliver, MD, and colleagues used this approach but used only air instead of gas with shorter postoperative prone positioning. The postoperative VA results were similar to other techniques. Minimizing post-operative prone positioning improves patient satisfaction and compliance.[27] Improving compliance with prone positioning in pneumatic patients is important for treatment success. Harvey Lincoff, MD, and colleagues investigated the efficacy of 40 degrees gaze down rather than face-down positioning and found it to be just as effective and considerably more tolerable.[28]

Because submacular hemorrhage is the result of abnormal vasculature, most often from AMD, visual stability over time is dependent on the control of the underlying disease.[5,6,10] This has prompted the investigation of adjuvant anti-VEGF therapy in the surgical treatment of submacular hemorrhage. A few case reports show favorable results in the patients receiving intravitreal anti-VEGF injections in both pneumatic displacement alone and following PPV.[2,9]

Recently, a large case series from our institution looked at 101 cases of submacular hemorrhage treated with PPV/subretinal t-PA/pneumatic gas displacement with and without postoperative anti-VEGF injections and found that 82 percent of the eyes had improvement in postoperative VA. Approximately 40 percent received anti-VEGF therapy, and these eyes showed greater VA improvement six months after surgery than those who did not receive anti-VEGF injections. The authors concluded that the addition of anti-VEGF might reduce disease progression and maintain gains made by the initial removal of submacular hemorrhage.

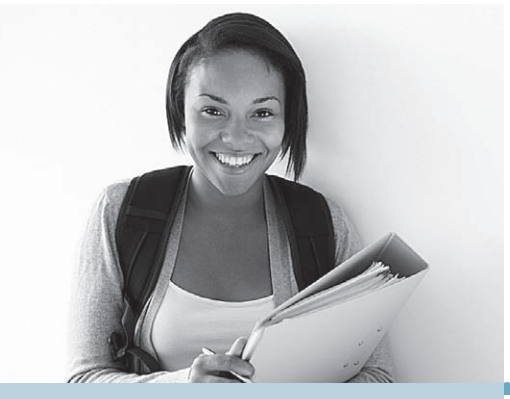




The Rick Bay Foundation

for Excellence in Eyecare Education

www.rickbayfoundation.org

Support the Education of Future Healthcare & Eyecare Professionals



About Rick

Rick Bay served as the publisher of The *Review* Group since 1991.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships will be awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and will be chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

Interested in being a partner with us?

Visit www.rickbayfoundation.org

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education

(Garg SJ, et al. Subretinal t-PA with Pneumatic Displacement With and Without Intravitreal Anti-VEGF Agents for the Treatment of Thick Subretinal Hemorrhage Due to Exudative Age-related Macular Degeneration. The Retina Society. September 25, 2011. Rome, Italy.)

Figure 4. Small 41-ga. microcannula used to create the retinotomy for subretinal t-PA injections.

The pharmacokinetics in eyes that have had PPV differ from those that have not had PPV. Medications including anti-VEGF agents might have a shorter half-life in vitrectomized eyes, and diffusion across the SMH may be impaired. To counter this, a few case series have investigated the efficacy of subretinal anti-VEGF injections. Felix Treumer, MD, and colleagues evaluated PPV with subretinal bevacizumab and t-PA followed by pneumatic displacement and found the technique was safe and effective at displacing the hemorrhage and improving VA.[29]

Studies investigating adjuvant anti-VEGF therapy, either intravitreal or subretinal, suggest that postoperative treatment should include aggressive management of the underlying etiology in order to maintain the visual gains following displacement of the hemorrhage. In the case of AMD, this involves close observation and often maintenance therapy with intravitreal anti-VEGF injections.[29]

Submacular hemorrhage is a potentially visually devastating condition most commonly associated with CNVM due to AMD. Given its poor natural course, various treatment options have been tried with variable degrees of success. As in all diseases, patient selection is paramount. Office-based procedures such as t-PA-assisted pneumatic displacement or anti-VEGF monotherapy offer some chance of visual improvement with a minimally invasive approach. Submacular surgery has been largely replaced by PPV and pneumatic displacement with or without the assistance of t-PA and anti-VEGF injections.

These techniques appear to be reasonably effective, but require good surgical candidates. Even with surgery, the underlying disease must be managed and the post-surgical addition of anti-VEGF medications appears to help preserve vision over time. Although the visual outcome in these patients varies widely, these strategies can help improve vision in some patients. REVIEW

Dr. Driscoll is co-chief resident of ophthalmology at Wills Eye Institute. Dr. Garg is an associate professor of ophthalmology on the Retina Service of Wills Eye Hospital and practices at MidAtlantic Retina. He can be contacted at 1 (800) 331-6634 or sgarg@midatlanticretina.com.

1. Shultz RW, Bakri SJ. Treatment for submacular hemorrhage associated with neovascular age-related macular degeneration. Semin Ophthalmol 2011;26(6):361-71.
2. Skaf AR, Mahmoud T. Surgical treatment of age-related macular degeneration. Semin Ophthalmol 2011;26(3):181-91.
3. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina 1996;16:183-9.
4. Bakri SJ, Nickel J, Yoganathan P, Beer PM. Photodynamic therapy for choroidal neovascularization associated with submacular hemorrhage in age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2006;37(4):278-83.
5. Hassan AS, Johnson MW, Schneiderman TE, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. Ophthalmology 1999;106:1900-6; discussion 6-7.
6. Hesse L, Schmidt J, Kroll P. Management of acute submacular hemorrhage using recombinant tissue plasminogen activator and gas. Graefe's Arch Clin Exp Ophthalmol 1999;237(4):273-7.
7. Chen CY, Hooper C, Chiu D, et al. Management of submacular hemorrhage with intravitreal injection of tissue plasminogen activator and expansile gas. Retina 2007;27:321-8.
8. Ohji M, Saito Y, Hayashi A, et al. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. Arch Ophthalmol 1998;116:1326-32.
9. Steel DH, Sandhu SS. Submacular haemorrhages associated with neovascular age-related macular degeneration. Br J Ophthalmol 2011;95(8):1051-7.
10. Johnson MW. Pneumatic displacement of submacular hemorrhage. Curr Opin Ophthalmol 2000;11(3):201-6.
11. Ratra D, Basia A. Intravitreous tissue plasminogen activator with pneumatic displacement in submacular hemorrhage. Arch Ophthalmol 2012;130:795-6.
12. Cakir M, Cekic O, Yilmaz OF. Pneumatic displacement of acute submacular hemorrhage with and without the use of tissue plasminogen activator. Eur J Ophthalmol 2010;20(3):565-71.
13. Chen SN, Yang TC, Ho CL, et al. Retinal toxicity of intravitreal tissue plasminogen activator: case report and literature review. Ophthalmology 2003;110:704-8.
14. Gopalakrishan M, Giridhar A, Bhat S, et al. Pneumatic displacement of submacular hemorrhage: safety, efficacy, and patient selection. Retina 2007;27:329-34.
15. Kamei M, Misono K, Lewis H. A study of the ability of tissue plasminogen activator to diffuse into the subretinal space after intravitreal injection in rabbits. Am J Ophthalmol 1999;128(6):739-46.
16. Coll GE, Sparrow JR, Marinovic A, Chang S. Effect of intravitreal tissue plasminogen activator on experimental subretinal hemorrhage. Retina 1995;15:319-26.
17. Hattenbach LO, Klais C, Koch FH, Gumbel HO. Intravitreous injection of tissue plasminogen activator and gas in the treatment of submacular hemorrhage under various conditions. Ophthalmology 2001;108:1485-92.
18. Shienbaum G, Garcia Filho CA, Flynn HW Jr., et al. Management of Submacular Hemorrhage Secondary to Neovascular Age-Related Macular Degeneration With Anti-Vascular Endothelial Growth Factor Monotherapy. Am J Ophthalmol 2013;155:1009-13. doi: 10.1016/j.ajo.2013.01.012. Epub 2013 Mar 7.
19. Stifter E, Michels S, Prager F, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol 2007;144:886-92.
20. Chang MA, Do DV, Bressler SB, et al. Prospective one-year study of ranibizumab for predominantly hemorrhagic choroidal neovascular lesions in age-related macular degeneration. Retina 2010;30:1171-6.
21. Kamei M, Tano Y. Tissue plasminogen activator-assisted vitrectomy: surgical drainage of submacular hemorrhage. Dev Ophthalmol 2009;44:82-8.
22. de Juan E Jr., Machemer R. Vitreous surgery for hemorrhagic and fibrous complications of age-related macular degeneration. Am J Ophthalmol 1988;105:25-9.
23. Wade EC, Flynn HW Jr., Olsen KR, et al. Subretinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch Ophthalmol 1990;108:973-8.
24. Vander JF. Tissue plasminogen activator irrigation to facilitate removal of subretinal hemorrhage during vitrectomy. Ophthalmic Surg 1992;23(5):361-3.
25. Bressler NM, Bressler SB, Childs AL, et al. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. Ophthalmology 2004;111:1993-2006.
26. Haupert CL, McCuen BW, 2nd, Jaffe GJ, et al. Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. Am J Ophthalmol 2001;131:208-15.
27. Olivier S, Chow DR, Packo KH, et al. Subretinal recombinant tissue plasminogen activator injection and pneumatic displacement of thick submacular hemorrhage in age-related macular degeneration. Ophthalmology 2004;111:1201-8.
28. Lincoff H, Kreissig I, Stopa M, Uram D. A 40 degrees gaze down position for pneumatic displacement of submacular hemorrhage: clinical application and results. Retina 2008;28:56-9.
29. Treumer F, Roider J, Hillenkamp J. Long-term outcome of subretinal coapplication of rtPA and bevacizumab followed by repeated intravitreal anti-VEGF injections for neovascular AMD with submacular haemorrhage. Br J Ophthalmol 2012;96(5):708-13.

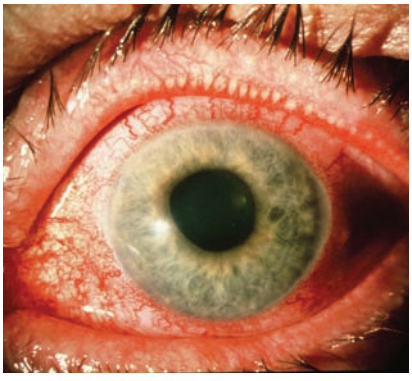
Systemic Rxs And Ocular AEs

When a patient is taking drugs systemically, here are the ocular adverse events to be on the lookout for.

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

Our old pharmacology professor used to hammer us with the adage that "every drug has two effects: the one you know and the one you don't." Although untold numbers of medical students' eyes have rolled at hearing this cliché, practicing clinicians are aware that it's probably more accurate to pluralize the platitude to "the ones you know and those you don't." Routine perusal of the ophthalmology literature invariably turns up new associations between drugs and their unintended effects, but it's particularly difficult to stay up-to-date when it comes to the multitude of new systemic medicines and therapeutic combinations. This month we provide a refresher course on the adverse ocular effects of systemic medications, and highlight a few newer drugs or drug classes with suspected or confirmed ocular off-effects.

Classifying the adverse effects of drugs can be done according to any number of criteria, but one approach we find useful is to subdivide the list of AEs into those in which adverse effects are therapeutically related or class-specific, and those that are more idiosyncratic or associated with a single therapeutic entity. This distinction is useful when charting a course of action to minimize an adverse effect. While there's no convincing evidence that switching a patient from Lipitor to Zocor will alter risk of cataract, recommending a second-generation anti-histamine over a first-generation drug might be all that's needed to alleviate a patient's dry eye. In addition, AEs that are class-specific are more likely to be dose-dependent, so it may be possible to titrate medications to an optimal level where therapeutic effects are retained but untoward actions are eliminated or minimized.



Angle-closure glaucoma is a rare adverse effect of the systemic drug topiramate.

Once a drug attains Food and Drug Administration approval and is brought to market, the process of identifying significant AEs begins in earnest. That may sound odd, but the drug approval process can only identify the most prominent of potential AEs, such as those that occur in short courses or in a high percentage of patients; these are usually modest for drugs that achieve final approval. With post-approval monitoring comes the ability to track use in millions of patients over years of use. Often, AEs that are identified following approval are then examined in controlled trials, either prospectively or using established longitudinal databases such as the Beaver Dam Eye Study.[1] Availability of these databases allows investigators to address questions of long-term drug effects in large populations, and these questions often have surprising answers.

An example of an AE revealed by a longitudinal database involves the statins, a class of drugs that have revolutionized treatment of lipid disorders, diabetes and cardiovascular disease. Since its approval in 1996, atorvastatin became the best-selling

This article has no commercial sponsorship.

drug ever, and led to the development of many bio-similars. While they are thought to act primarily by reducing cholesterol biosynthesis via inhibition of HMG-coA reductase, statins clearly have effects on other oxidative pathways and were hypothesized to promote a host of beneficial effects in this way. Among these other benefits was a reported reduction in cataract formation, with a particular effect on nuclear cataracts.[2,3] Several retrospective studies provided evidence to support this idea, but recently the tide is flowing in the opposite direction: Rather than a protective effect, statins seem to increase the risk of cortical cataracts.[4] Clearly, since these drugs are prescribed for serious medical conditions there has to be a comprehensive cost-benefit assessment when a patient receiving statin therapy displays early signs of cataract formation.

Another example of a therapeutic heavyweight with potential for ocular AEs is the bisphosphonates, drugs such as alendronate that are first-line therapy for prevention and treatment of osteoporosis. Ocular side effects associated with these drugs include anterior uveitis and scleritis, and although these effects do not seem to be related to the drugs' mechanism of action (inhibition of bone resorption by osteoclasts) they are dose-related.[5-7] In contrast to the example of statins, it would seem difficult to justify use of a drug for prevention of disease when it induces other, potentially more serious eye disorders. It's important to note, however, that ocular AEs seem to be limited to the most potent of the bisphosphonates, particularly pamidronate and zoledronate.

An important class of drugs linked to ocular side effects is the thiazolidinediones, drugs used to treat type-2 diabetes that activate the peroxisome proliferator-activated receptor pathways involved in glucose utilization. A number of studies have linked these compounds to an increased risk of macular edema, but there is still some debate as to the significance of these effects.[8,9] Since there are other drugs available, patients with other risk factors for macular disease might be best served by avoiding this class of diabetes medications.

Adverse Ocular Effects Associated with Systemic Medications

Drug/Drug Class	Examples	Adverse effects
		Confirmed
antihistamines	Claritin, Benadryl	Dry eye
anti-depressants	Zoloft, doxepin	
anti-psychotics/neuroleptics	Abilify, Risperdal, Clozaril	
alpha-adrenergic antagonists	tamsulosin, alfuzosin, doxazosin	floppy iris syndrome
bisphosphonates	zoledronate, pamidronate	anterior uveitis
corticosteroids	dexamethasone, prednisone	cataract, elevated IOP
phosphodiesterase type 5 inhibitors	sildenafil, vardenafil	visual disturbances, arteritis, other ischemic events
		Suspected
thiazolidinediones (PPAR-gamma agonists)	rosiglitazone	macular edema
statins	simvastatin, atorvastatin	cataracts, myopathies
		Reported
TNF-α inhibitors	etanercept	uveitis
EGF receptor kinase inhibitors	erlotinib	corneal ulceration/perforation
PI3K/Akt/mTOR inhibitors	perifosine	corneal infiltrates

Anti-cholinergic Effects

The most common of all systemic drug side effects are, unquestionably, those referred to as anti-cholinergic. It might be more accurate to refer to these adverse responses as anti-muscarinic, since they result from the blockade of muscarinic cholinergic receptors of the parasympathetic nervous system.[10] These include pathways that control heart rate, lacrimal and salivary secretion, urine flow and gastro-intestinal motility. Anti-cholinergic drug side effects are often the first place clinicians look when faced with a patient complaining of constipation, dry mouth or dry eye.

Class-specific adverse effects have been reported with alpha-adrenergic antagonists such as tamsulosin, alfuzosin, doxazosin or terazosin that are used to treat benign prostatic hyperplasia. These drugs can cause floppy iris syndrome and are also associated with problems with blurred vision.[10] These issues represent a classic case of "forewarned is forearmed": As long as we are aware of the patient's medication usage, a modified game plan can usually prevent or minimize hazards associated with surgical complications caused by IFIS.

While anti-cholinergic AEs may be the most common, perhaps the most significant ocular AEs ophthalmologists deal with on a daily basis are those that stem from systemic

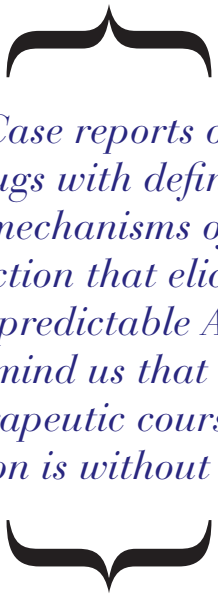
glucocorticoid use.[10] Ophthalmic use of steroids relies on topical formulations which allow for the combination of high doses and short courses that can mitigate the risks associated with these agents, including increases in intraocular pressure and cataract formation. In contrast, patients receiving long-term systemic steroid therapy need to be monitored for these serious actions of steroid use.

The Unexpected AE

Examples in recent literature show that, ultimately, it's impossible to predict with certainty how each patient will respond to therapeutic intervention. Case reports of drugs with clearly defined mechanisms of action that elicit completely unpredictable AEs remind us that no therapeutic course of action is without risk. A recent report described an apparent drug-induced corneal ring infiltrate that progressed rapidly and responded to treatment efforts poorly.[11] The patient was receiving an investigational anti-cancer drug (perifosine); in such cases it is not even possible to state with certainty that the drug was the causative agent. Many such case reports reflect extremely rare AEs, yet it's worth remembering that the rare case can still be our patient.

A classic example of an idiosyncratic AE occurs with topiramate, a drug originally developed as an antiepileptic that acts by interfering with voltage- and ligand-gated ion channels.[12] While this mechanism of action is similar to many other drugs used for seizure disorders, only topiramate has been associated with cases of bilateral angle-closure glaucoma, which, although rare, is an ophthalmic emergency that can lead to loss of vision. Despite this, topiramate has gained a host of new indications in recent years, including migraine, bipolar disorder and neuropathic pain.

Another unexpected AE is the case of the anti-TNF-α mAb etanercept, a drug that is used in several types of inflammatory conditions (arthritis, psoriasis) yet has been associated with ocular inflammation, including uveitis and scleritis.[13] These reactions occurred in patients with rheumatic disease but no sign of ocular involvement prior to etanercept therapy, and in all reported cases the condition resolved upon withdrawal of the drug.



Among the newer groups of biological therapeutics, epidermal growth factor receptor kinase inhibitors such as gefitinib, erlotinib, sorafenib and sunitinib have been associated with severe but rare cases of corneal perforation.[14] These drugs are used to treat various solid tumors and represent a significant therapeutic advance over previous therapies. An interesting aspect of their mechanism of action stems from the targeting of tumor-specific genotyping of EGFR polymorphisms that may be useful in selecting which agent to use in specific patients;[15] this same technique may hold promise as a means to predict those at risk for adverse effects, and thus provide a way to avoid the unfavorable sequelae of therapy.

The promise of personal genetics in medicine isn't just about deriving ideal treatments to address an individual patient's condition, but also to predict and to avoid potential drug AEs. This approach is already in development for mitigating risk of severe AEs such as Stevens-Johnson syndrome,[16] but may be suitable for a more customized usage in the future. Genomic approaches, as well as the more traditional clinical rigor, are tools needed to uphold another of those medical clichés: Above all, do no harm. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. McLaughlin is a medical writer at Ora Inc.

1. http://www.bdeyestudy.org/ accessed 2 Oct 2013.
2. Klein BE, Klein R, Lee KE, Grady LM. Statin use and incident nuclear cataract. JAMA 2006;295:23:2752-8.
3. Hermansa MB, Ahnb SA, Rousseau MF. Statin therapy and cataract in type 2 diabetes. Diabetes & Metabolism. 2011; 37:139–143.
4. Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I. Association of statin use with cataracts: A propensity score-matched analysis. JAMA Ophthalmol 2013. doi: 10.1001/jamaophthalmol.2013.4575. [Epub ahead of print]
5. Pazianas M, Clark EM, Eiken PA, Brixen K, Abrahamsen B. Inflammatory eye reactions in patients treated with bisphosphonates and other osteoporosis medications: Cohort analysis using a national prescription database of systemic drugs with ocular adverse effects. J Bone Mineral Res 2013;28:455-463.
6. Dipika V. Patel DV, Horne A, House M, Reid IR, McGhee CN. The incidence of acute anterior uveitis after intravenous zoledronate. Ophthalmology 2013;120:773–776.
7. Etminan M, Forooghian F, Maberley D. Inflammatory ocular adverse events with the use of oral bisphosphonates: A retrospective cohort study. CMAJ 2012;184:8:E431-4.
8. Singh S, Segal JB. Thiazolidinediones and Macular Edema. Arch Intern Med 2012;172:1011-1013.
9. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med 2012;172:13:1005-1011.
10. Li J, Tripathi RC, Tripathi BJ. Drug-induced ocular disorders. Drug Safety 2008;31:127-141.
11. Keenan JD, Fram NR, McLeod SD, Strauss EC, Margolis TP. Perifosine-related rapidly progressive corneal ring infiltrate. Cornea 2010;29:583–585.
12. Abtahi MA, Abtahi SH, Fazel F, Roomizadeh P, et al. Topiramate and vision: A systematic review. Clin Ophthalmol 2012;6:117-31.
13. Gaujoux-Viala C, Giampietro C, Gaujoux T, et al. Scleritis: A paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. J Rheumatol 2012;39:2:233-9.
14. Borkar DS, Lacouture ME, Basti S. Spectrum of ocular toxicities from epidermal growth factor receptor inhibitors and their intermediate-term follow-up: A five-year review. Support Care Cancer 2013;21:4:1167-74.
15. Erdem L, Giovannetti E, Leon LG, Honeywell R, Peters GJ. Polymorphisms to predict outcome to the tyrosine kinase inhibitors gefitinib, erlotinib, sorafenib and sunitinib. Curr Top Med Chem 2012;12:15:1649-59.
16. Wei CY, Lee MT, Chen YT. Pharmacogenomics of adverse drug reactions: Implementing personalized medicine. Hum Mol Genet 2012;21:R1:R58-65.

REVIEW® of Ophthalmology

Ophthalmic Resources Online

This service allows you to capture needed measures for two meaningful use objectives:

1) electronic transmission of patient prescriptions

2) distribution of patient-specific education materials

ECP Resources and ePrescribing from *Review of Ophthalmology* and Healthcare Resources Online enable you to provide patient education, electronic prescribing and generate reports that allow you to attest for meaningful use incentives; however, determination of your bonus payments from CMS depends on other factors and qualifications specific to your practice.

For More Information, Visit Our MD E-Prescribing Resources Page:

www.revophth.com/MD_Resources_eRX/

Download a QR scanner app. Launch app and hold your mobile device over the code and get ready to view our website.


Hysteresis: A Powerful Tool for Glaucoma Care

Clinical data suggests that this measurement may be a valuable indicator of risk—and how a patient will respond to medication.

Nathan M. Radcliffe, MD, New York City

Managing glaucoma is a challenge, and an additional tool is always welcome. In recent years, a new instrument (Reicherts's Ocular Response Analyzer) has brought to light a previously unmeasured corneal characteristic—hysteresis—that is turning out to have multiple clinical uses. Not only does it appear to provide a measurement of intraocular pressure that's less affected by factors such as undergoing LASIK, it is also showing an ability to help manage glaucoma, offering valuable information regarding which patients are more at risk of progression and which patients will respond more to topical medications.

Here, I'd like review some of the recent clinical data regarding hysteresis, discuss possible explanations for what is actually being measured and talk about how measuring corneal hysteresis may be a significant aid when caring for glaucoma patients and suspects.

What Are We Measuring?

A good place to start is by asking the question: When we measure hysteresis, what exactly are we measuring? Technically, hysteresis is defined as the difference between the pressure at which the cornea bends inward during an airjet applanation and the pressure at which it bends out again. *(See diagram, facing page.)* It's thought that this difference, which is measured in mmHg, gauges a biomechanical property of the cornea relating to its elasticity—specifically, the cornea's relative ability to absorb pressure by bending when pressure is applied.

Given this specific definition of hysteresis, it can currently only be measured by the Ocular Response Analyzer. However, there's another device produced by Oculus, called the Corvis ST, which like the ORA device uses an airjet tonometer to measure pressure. Unlike the ORA, it uses a high-speed Scheimpflug camera to monitor the cornea while the pressure is being measured, and it can calculate all sorts of other parameters. Essentially, like the Reichert instrument, it's trying to measure the biomechanical properties of the cornea. Whether it actually measures the parameter we call hysteresis or something different remains to be seen. We're waiting for more data from that device.

Thickness and Hysteresis

As you know, corneal thickness has become important in the management of glaucoma. Given that both thickness and hysteresis are corneal factors, comparing their histories, uses and interaction provides some interesting insights into the nature and value of hysteresis.

Corneal hysteresis and corneal thickness share some interesting parallels. Ophthalmologists became interested in corneal thickness initially because it was thought to be a factor that interfered with our ability to accurately measure IOP, particularly when using Goldmann applanation tonometry. (The Goldmann technology was developed with the assumption that corneal thickness was relatively constant from one person to the next, which turned out not to be the case.) To our surprise, studies like the Ocular Hypertension Treatment Study revealed that corneal thickness was an

independent risk factor for glaucoma progression. For example, a drop in 40 µm of corneal thickness equates with about a 70-percent higher chance of developing glaucoma. That means that a thicker cornea may be more than sufficient to offset the risk associated with a higher pressure. A person who has a pressure of 30 mmHg with a corneal thickness of 600 µm has half the glaucoma risk of someone who has a pressure of 20 mmHg—10 mmHg less—if that person also has a corneal thickness of 500 µm. In other words, in terms of glaucoma risk, the cornea is just as important a factor to consider as the IOP.

In certain respects, our understanding of corneal hysteresis has followed the same path as corneal thickness. Researchers were interested in hysteresis initially as a means to help doctors more accurately measure IOP. That work was fruitful; for example, some of the early work demonstrated that when IOP was adjusted for hysteresis it would measure the same before and after LASIK—not the case with methods such as Goldmann tonometry. As a result of that data, they began to recommend the Ocular Response Analyzer as a way to accurately measure IOP. Ironically, that may have ended up being a distraction, because like corneal thickness, most of the accumulating data is showing hysteresis to be a risk factor for glaucoma—even a more significant risk factor than corneal thickness.

This raises the question: Are corneal thickness and hysteresis related? They do correlate to a small degree, but they are definitely not the same thing. Some people have thick corneas and low hysteresis; other have the reverse. However, both go down with age. Furthermore, in a study I conducted, we found that African Americans and Hispanics have lower hysteresis than Caucasians.[1] In the OHTS study, one of the main factors that accounted for glaucoma risk in blacks was a thin cornea; it turns out they have lower hysteresis as well.

The measurement of corneal hysteresis has been slow to be adopted clinically compared to a corneal parameter such as pachymetry. However, corneal pachymetry was quickly adopted for several reasons that haven't applied to hysteresis. For one thing, the largest glaucoma study (the OHTS, which involved 1,600 patients) validated pachymetry's clinical usefulness. For another thing, devices that measure pachymetry are often portable and relatively inexpensive, and pachymetry measurements can be performed by many devices using several techniques. That made it easier for people to start measuring corneal thickness, get comfortable with it and eventually adopt it into their practices.

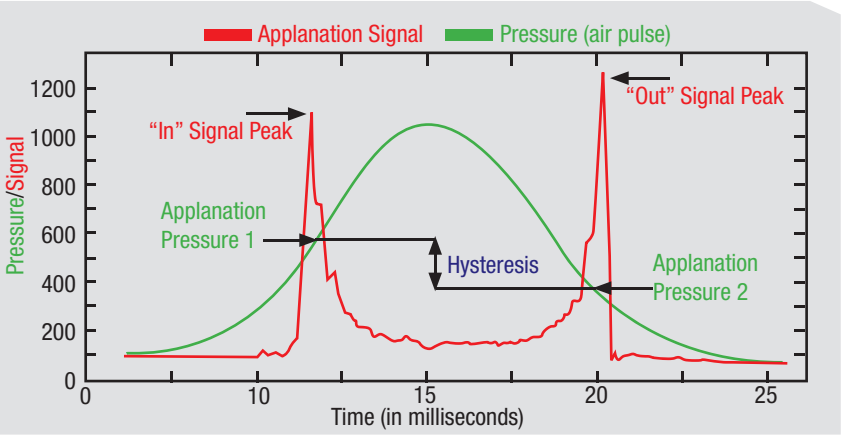
The Progression Connection

One of the most important things we've learned about hysteresis is that a low hysteresis correlates with a greater risk of glaucoma progression. Several studies have confirmed this association. A study by the Chinese University of Hong Kong's Nathan Congdon, MD, and Wilmer Eye Institute's Harry Quigley, MD,[2] as well as a paper by New York University Medical Center ophthalmologist Gustavo deMoraes,[3] showed that patients with lower hysteresis were more likely to have progression, as evidenced by visual fields. Also, I recently completed a study that showed that having a lower hysteresis was also associated with progression in terms of optic nerve damage.[4]

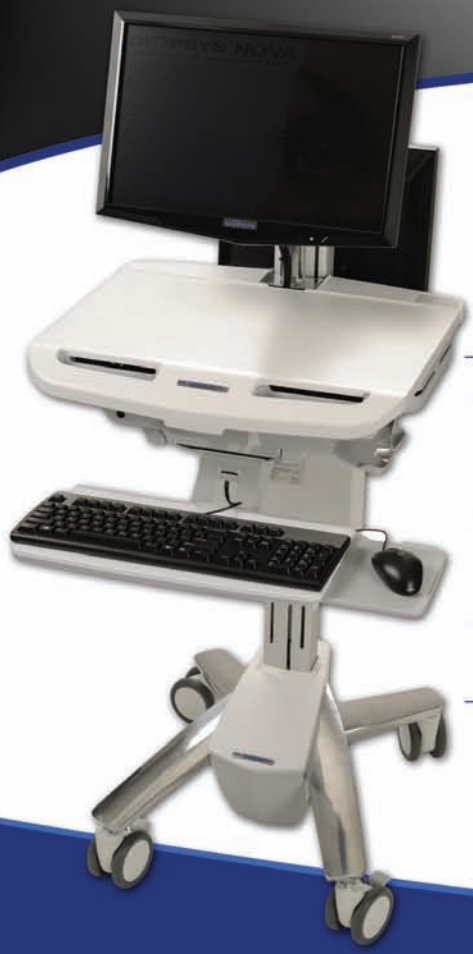
Corneal thickness has been tied to risk of progression, but in the three studies mentioned above that compared hysteresis and corneal thickness, hysteresis has turned out to be a more powerful predictor of progression. All three of those studies were large and had significant numbers, although they were all retrospective studies, which means that technically, hysteresis was associated with progression rather than being an established risk factor.

To be able to define something as a risk factor, you have to collect the hysteresis first and then follow patients for four years or so. Drs. Felipe A. Medeiros, MD, PhD, and Robert

How Hysteresis Is Determined



Corneal hysteresis is defined as the difference between the pressure at which the cornea bends inward during an airjet applanation and the pressure at which it bends out again, as determined by an infrared laser during an intraocular pressure measurement. This appears to quantify a biomechanical property of the cornea relating to its elasticity.



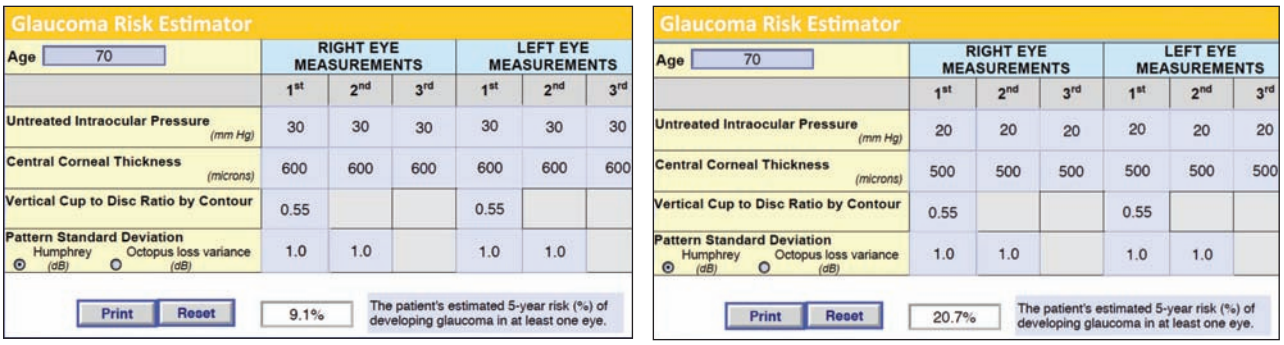
The company that brought VEP into the eye care practice now leads the way to office-based pattern ERG.

- The new Diopsys® NOVA-ERG test helps doctors assess retinal function while VEP helps assess the entire visual pathway.
- Easy-to-use ERG Lid Sensors are comfortable for the patient and convenient for the doctor.
- Reimbursement for CPT Codes 95930 (VEP) & 92275 (ERG) can each exceed $100.*

To learn more, visit *www.PatternERG.com*

DIOPSYS® NOVA-VEP
OFFICE BASED VISUAL EVOKED POTENTIAL TESTING

*Insurance coverage may vary by contract. Please contact Diopsys at 973-244-0622 for more detail on coverage.



Glaucoma Risk Estimator

Age 70	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure (mm Hg)	30	30	30	30	30	30
Central Corneal Thickness (microns)	600	600	600	600	600	600
Vertical Cup to Disc Ratio by Contour	0.55			0.55		
Pattern Standard Deviation (Humphrey (dB) / Octopus loss variance (dB))	1.0	1.0		1.0	1.0	

Print | Reset | 9.1% | The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

Glaucoma Risk Estimator

Age 70	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure (mm Hg)	20	20	20	20	20	20
Central Corneal Thickness (microns)	500	500	500	500	500	500
Vertical Cup to Disc Ratio by Contour	0.55			0.55		
Pattern Standard Deviation (Humphrey (dB) / Octopus loss variance (dB))	1.0	1.0		1.0	1.0	

Print | Reset | 20.7% | The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

Although it's tempting to react to a patient's IOP as an isolated number, corneal characteristics dramatically impact the risk associated with a given pressure. Above, the Glaucoma 5-Year Risk Estimator (based on the Ocular Hypertension Treatment Study and European Glaucoma Prevention Study) shows that an eye with a central corneal thickness of 600 µm and an IOP of 30 mmHg has a 9.1-percent risk of developing glaucoma; an eye with a lower IOP of 20 mmHg—but a thinner, 500-µm-thick cornea—has a 20.7-percent risk.

N. Weinreb, MD, of the University of California, San Diego, recently conducted such a prospective study, involving 114 eyes of 68 patients.[5] They collected hysteresis at baseline and then followed the patients for an average of four years so they could determine whether or not hysteresis was a risk factor for glaucoma progression. They found that visual fields of patients whose hysteresis was 4 mmHg or lower tended to degrade at a faster rate; also, the patients with low hysteresis and high pressures were at the greatest risk. Furthermore, hysteresis accounted for three times as much of the progression as corneal thickness.

Interestingly, one of the strongest and most consistently demonstrated risk factors for progression in all of the literature is age. And sure enough, as you age, your hysteresis score drops. In fact, if you take the patient's age into account in some of these studies, the hysteresis effect is a little bit weaker, although it's still present. So there is some interplay between age and hysteresis.

The IOP Connection

One important difference between hysteresis and corneal thickness is that corneal thickness is almost always very similar, if not identical, between the two eyes; it doesn't change very much based on your eye pressure. In contrast, hysteresis will often vary, and it does change when IOP changes. For example, hysteresis is lower when an eye has higher pressure, so starting a patient on a drop should both lower her pressure and raise her hysteresis a little bit. Corneal hysteresis is not an inherent property of a cornea; it's more like a behavior.

The fact that IOP and corneal hysteresis interact is both potentially helpful and harmful from a clinical standpoint. Because it can change so readily, it may not be as repeatable a measurement. On the other hand, we may get more information from measuring it once we know why it's higher one day and lower another day. In fact, the interplay between IOP and hysteresis suggests to me that hysteresis might be useful as a clinical target. At some point it is conceivable that we may be focusing on trying to get our patient's hysteresis to a particular level, just as we now try to do with IOP.

At the same time, the interaction between hysteresis and pressure makes the equation complex. If a patient has very high pressure—say 35 mmHg—and his hysteresis is very low, both are associated with increased risk, but which is of more concern? (As someone who has measured hysteresis clinically for some time, I often find that hysteresis is more closely related to a patient's risk of worsening than his IOP.)

The Medication Effect

Another fascinating fact relating to hysteresis is that it can give you some idea of how much a person's pressure will come down when you start him on an eye drop. In one recent study we found that if a patient has a very low hysteresis, for example 7 mmHg, putting him on a medication might produce a 29-percent pressure reduction. But if the patient has a high hysteresis, such as 11.9 mmHg, that patient would only get 7.6-percent pressure reduction from the same medication.[6] *(See charts, p. 55.)*

Knowing this could be helpful, because sometimes when the pressure doesn't come down we're tempted to start the patient on a second drop. If you know the patient has a high hysteresis, you know that the patient has a lower risk of progression—and, you know that you may not see a big pressure drop when you start a new medicine. In this situation, I can take a step back; instead of adding more drops, I'll just watch the patient and see if he progresses. Conversely, when a patient with a low hysteresis has a nice pressure response to a new drop, that's good news; but you can't let your guard down. The low hysteresis means the patient is at greater risk, so

BEST HOSPITALS
U.S.News & WORLD REPORT
HONOR ROLL
2013-14

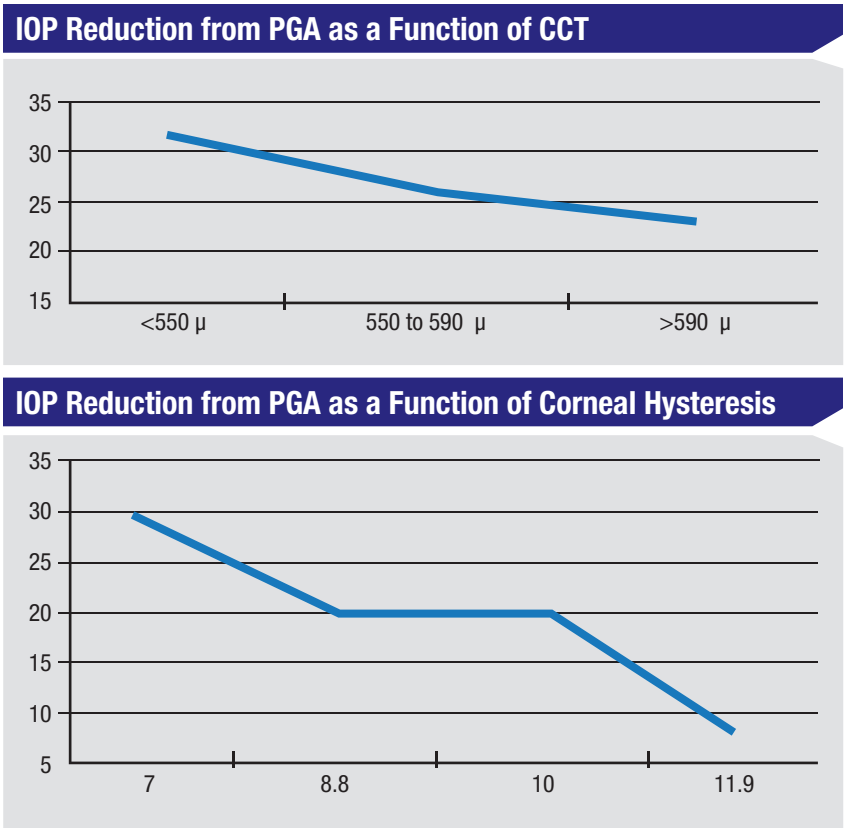
WE'RE CHANGING THE WAY

PATIENTS WITH VISION IMPAIRMENT ENVISION THEIR FUTURE

The Louis J. Fox Center for Vision Restoration of UPMC and the University of Pittsburgh—a joint program of the UPMC Eye Center and the McGowan Institute for Regenerative Medicine—is the first national, comprehensive, and multidisciplinary research and clinical program dedicated to ocular regenerative medicine. Our ophthalmologists and researchers focus on the discovery of new treatments for blindness and impairment through tissue regeneration, enhancement, transplantation, and technology. We're working hard to improve the quality of life for the millions of people affected by vision loss, so that we can all see a brighter future. Learn more at **UPMCPhysicianResources.com/Vision.**

UPMC LIFE CHANGING MEDICINE

UPMC is affiliated with the University of Pittsburgh School of Medicine.



The extent of IOP reduction produced by a prostaglandin analogue has been shown to correlate with central corneal thickness (top chart). However, the degree of medication response correlates even more strongly with corneal hysteresis (bottom chart). (Top chart based on Brandt JD, et al. Am J Ophthalmol 2004;138:5:717-22. Bottom chart based on Agarwal DR, et al. Br J Ophthalmol 2012;96:2:254-7.)

you still have to watch him carefully.

We set target pressures all the time, but the patient's cornea will actually tell us a lot about whether the patient will get to that target. Knowing that you might not need to add the extra drop is important because adding a drop punishes the patient; it's tough on the patient's lifestyle and tough on the eyes. You don't want to add a drop unless you really have to.

Incidentally, you might suspect that this difference in response to medication could be explained by the drop penetrating the cornea more or less effectively when the hysteresis is low or high. However, the data indicates otherwise, because the same association was recently found with selective laser trabeculoplasty.[7] Sixty-eight eyes had laser trabeculoplasty; the eyes were checked for both hysteresis and IOP. On average the SLT reduced the pressure 23 percent; but if you looked at who had the best response, those with higher pressure and lower hysteresis did the best. Those two factors accounted for 64 percent of the variability in pressure lowering.

So, hysteresis not only tells us something about a patient's risk of progressing, it also tells us a little bit about who might respond well—or not respond as well—to a drop (or to SLT).

One Possible Explanation

Obviously, all of this raises some important questions. What's happening in the cornea that produces a high or low hysteresis measurement? And how does the level of hysteresis increase or decrease the risk of glaucomatous progression?

Currently, we have no clear answers, only theories. One theory is that having a high corneal hysteresis is like having an eye that's a good shock absorber, for lack of a better term. When pressure is applied to a shock absorber, the shock absorber caves in a little to accommodate the increase in pressure. So an eye with high hysteresis may be more flexible, perhaps handling pressure more adroitly than a less-flexible eye with a lower hysteresis score, much like a flexible tree bending in the wind while a less-flexible tree is blown over and uprooted.

For example, one study found that when IOP was elevated, the optic nerve in patients with a high corneal hysteresis bowed back more than the optic nerve in people with lower hysteresis.[8] I recall reading the study and at first thinking that it made no sense. We don't want cupping; that's part of glaucoma. Why would I want the optic nerve to bow when the pressure increases? But eventually it dawned on me that if the nerve and cornea accommodate pressure by moving, rather than being rigid, it may actually reduce damage at the cellular level.

Furthermore, consider the fact that hysteresis drops when the intraocular pressure gets very high. That makes sense because an eye that has a high pressure is already under stress; it's already used up its ability to absorb energy or pressure. That eye, with its reduced flexibility, may be more susceptible to nerve damage. Conversely, when you lower the pressure, hysteresis increases; you've taken some stress out of the system. Now it has more absorbing capability again. Again, this is still theoretical.

ORA Parameters: Normals vs. Primary Open-Angle Glaucoma (mmHg)

	Caucasians		Africans		p-value
Parameter	Normal (n=25 eyes)	POAG (n=30 eyes)	Normal (n=30 eyes)	POAG (n=29 eyes)	
CH	10.8 ±1.6	9.2 ±1.8	9.2 ±1.5	8.3 ±1.7	<0.001
IOPcc	16.0 ±3.2	18.0 ±4.1	18.4 ±3.0	20.6 ±5.7	0.001
IOPg	15.6 ±3.3	16.4 ±5.0	16.7 ±3.7	18.4 ±5.8	NS

(CH = corneal hysteresis; IOPcc = corneal-compensated IOP; IOPg = Goldmann-correlated IOP; NS = not significant)

A comparison of normal eyes and eyes with primary open-angle glaucoma shows that the difference between their hysteresis and corneal-compensated IOP measurements is statistically significant; the difference in their Goldmann IOPs is not. (Based on Detry-Morel M, et al. Acta Ophthalmol 2012;90:2:118-24.)

Here's another way to think about this: Instead of giving us a simple reading of the pressure inside the eye, hysteresis may be telling us about the pressure the eye is experiencing. It's a bit like when my son and I carry our backpacks. He's lifting a lighter backpack, but it's heavier relative to his strength; so it feels heavier to him, and he's going to get tired sooner.

Knowing that bit of information might be far more useful in the real world than simply knowing the weight of the backpack. In other words, hysteresis may allow us to treat each eye as a unique entity. We already know that some eyes can handle high pressure and others can't; hysteresis might be the key to figuring out which ones are which. And all the data is consistent with that idea.

Hysteresis in the Clinic

So: How might a clinician use this measurement in practice to improve the care of glaucoma suspects and patients? As a clinician who has taken this measurement for several years, I can say that it does make a significant difference in my treatment decisions, and it's pretty easy to incorporate it into your routine.

Certainly, hysteresis tells me about a patient's risk, just as a thinner or thicker cornea does. A patient whose hysteresis is lower than, say, 9 mmHg is at greater risk of progression. If a patient has a higher hysteresis, I worry less, even if his pressure is elevated.

Hysteresis is helpful in glaucoma suspects because if the eye looks more cupped, has questionable nerve health or a suspicious visual field, and the hysteresis is lower in that eye, I see that as a pretty good evidence that the patient is at risk. The only thing I know of that connects an abnormal-looking nerve and low hysteresis is glaucoma. Notably, hysteresis is much more helpful in this situation than corneal thickness, because it's been shown that eyes with worse damage than the fellow eye will also have lower hysteresis than the fellow eye. In contrast, corneal thickness is almost always the same between the eyes, regardless of the levels of damage.

The interplay between hysteresis and medication response is also very clinically useful. Knowing a patient's hysteresis affects my expectations regarding how much of a pressure drop an eye will achieve on a new medication. For example, if a patient's hysteresis is high and his IOP doesn't drop much as a result of starting a medication, I know that this may be partly explained by the hysteresis. The medication is probably working better than it appears to be; I just can't measure it through the patient's cornea, which is absorbing so much energy. That realization prevents me from being hasty about starting the patient on an additional drop.

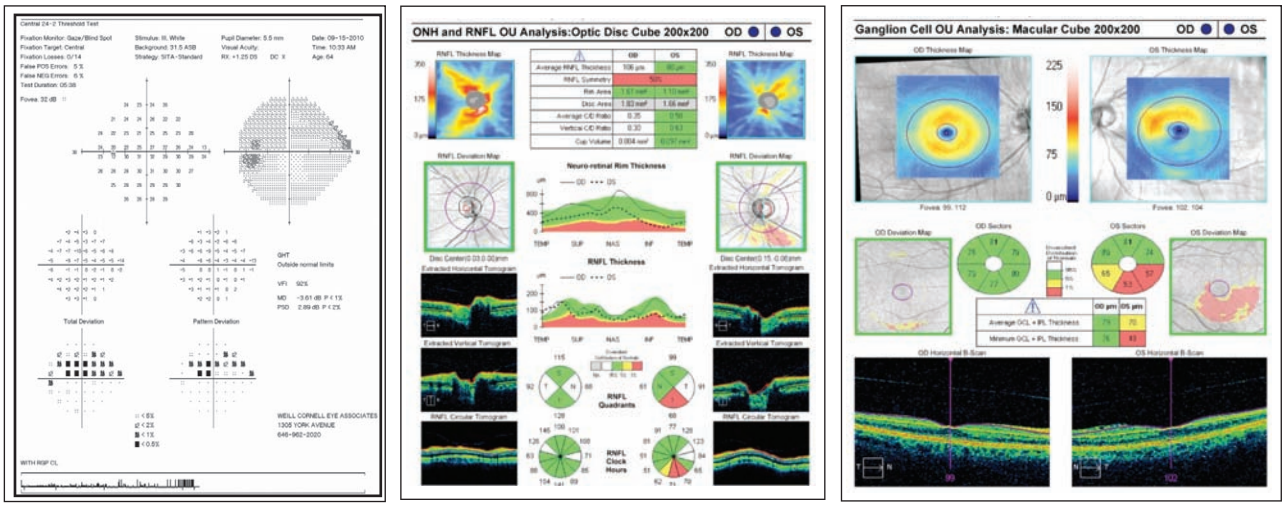
When a patient is at greater risk, I treat a low hysteresis the way I might treat a disc hemorrhage. It doesn't lead me into the operating room, but it may lead me to see the patient in three months instead of six. It may cause me to get two or three visual fields a year instead of just one. And it reminds me to make sure that I have all the information I need in case this patient does progress, including a picture of the optic nerve, visual fields and OCT data. If I have that high-quality information, I'll be able to detect the progression. (In fact, that's where the ball often gets dropped when managing glaucoma patients. We identify risk, but if we haven't been following the patient carefully, when he does progress we won't have confidence that the progression is real. Maybe the patient's first visual field wasn't high-quality and we neglected to repeat it; now we can't tell if we're seeing fluctuation or true progression. If we had just gotten more high-quality visual fields over a two-year period, we'd know.)

Hysteresis is also important when managing normal-tension glaucoma patients. In a study I conducted with New York City ophthalmologist Mitsugu Shimmyo, we found very low hysteresis in normal-tension glaucoma patients.[9] In that study we were looking at corneal-compensated IOP, i.e., pressure adjusted for hysteresis. After making that correction, we found that the normal-tension glaucoma patients actually had very high pressure. And the difference in pressure reading produced when this factor was taken into account was significantly greater in these patients than in high-tension patients or normals.

Put another way, some normal-tension glaucoma patients may not have normal tension at all.

Practical Realities

Undoubtedly, one factor that has



This 64-year-old patient presented with baseline intraocular pressures of 17 mmHg OD and 23 mmHg OS. Central corneal thickness in both eyes was 565 µm. Placing the patient on a beta blocker brought the IOP down to 18 mmHg OS; however, corneal hysteresis in that eye was 6.8—very low. (Hysteresis OD was 9.7—near normal.) Despite the patient's seemingly well-controlled IOP and thick cornea, the low hysteresis suggested the 18 mmHg might still leave the patient at risk, so the patient was switched to a prostaglandin analogue.

contributed to a very slow adoption of clinical hysteresis measurement is that it's not currently reimbursed by Medicare. In an ideal world that wouldn't matter, but doctors are hesitant to spend money on a device that will not be reimbursed. There is currently a tracking code for the measurement of corneal hysteresis (0181t), and it is reviewed by the Food and Drug Administration from time to time, so at some point it could become a standard code, allowing physicians to be reimbursed.

One interesting side effect of measuring hysteresis is that it often provides evidence that our previous analysis of a patient's situation was not accurate. That's fine if it indicates that the patient is not actually in as much danger as you thought; but if you start measuring corneal hysteresis, you're going to find that some patients are at much greater risk than you had previously recognized. That can be discouraging.

Nevertheless, measuring corneal hysteresis can be profoundly useful in the assessment of an individual's glaucoma risk, and it also provides an objective measurement of IOP. You don't have to worry about your technician having a bad day or be concerned that your hopes for this patient's pressure are biasing your measurements. With the ever-mounting evidence supporting the value of corneal hysteresis, I feel certain that one way or another this test will become incorporated into our standard clinical routine. And when it is, I believe it will change the way we practice.

Of course, we still don't understand exactly what it is we're measuring when we measure hysteresis. But as a doctor treating glaucoma, I'm ready to say that I'm not too concerned about what specific characteristic this measurement actually represents, because whatever it's measuring is meaningful. It's giving me important information about my patients' risk of progression, which has been validated by a number of well-executed, independent studies.

For that reason, I think we need to avoid becoming bogged down in the question of whether hysteresis is measuring viscous dampening or elasticity. For now, we can just note that it's measuring something that's important for glaucoma. We should start using it and learn more about it as we go along. REVIEW

Dr. Radcliffe is an assistant professor of ophthalmology at Weill Cornell Medical College in New York City. He has no financial ties to Reichert or the Ocular Response Analyzer.

1. Haseltine SJ, Pae J, Ehrlich JR, Shammas M, Radcliffe NM. Variation in corneal hysteresis and central corneal thickness among black, hispanic and white subjects. Acta Ophthalmol 2012;90:8:e626-31.
2. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol 2006;141:5:868-75.
3. De Moraes CV, Hill V, Tello C, Liebmann JM, Ritch R. Lower corneal hysteresis is associated with more rapid glaucomatous visual field progression. J Glaucoma. 2012;21:4:209-13.
4. Vu DM, Silva FQ, Haseltine SJ, Ehrlich JR, Radcliffe NM. Relationship between corneal hysteresis and optic nerve parameters measured with spectral domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol 2013;251:7:1777-83.
5. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology 2013;120:8:1533-40.
6. Agarwal DR, Ehrlich JR, Shimmyo M, Radcliffe NM. The relationship between corneal hysteresis and the magnitude of intraocular pressure reduction with topical prostaglandin therapy. Br J Ophthalmol 2012;96:2:254-7.
7. Hirneib C, Sekura K, Brandlhuber U, Kampik A, Kernt M. Corneal biomechanics predict the outcome of selective laser trabeculoplasty in medically uncontrolled glaucoma. Graefes Arch Clin Exp Ophthalmol 2013;251:10:2383-8.
8. Wells AP, Garway-Heath DF, Poostchi A, Wong T, Chan KC, Sachdev N. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. Invest Ophthalmol Vis Sci 2008;49:8:3262-8.
9. Ehrlich JR, Radcliffe NM, Shimmyo M. Goldmann applanation tonometry compared with corneal-compensated intraocular pressure in the evaluation of primary open-angle Glaucoma. BMC Ophthalmol 2012;12:52.

Insights from The ISRS Survey

This year's survey shows surgeons becoming more comfortable with the array of options available for correcting astigmatism.

Walter Bethke, Managing Editor

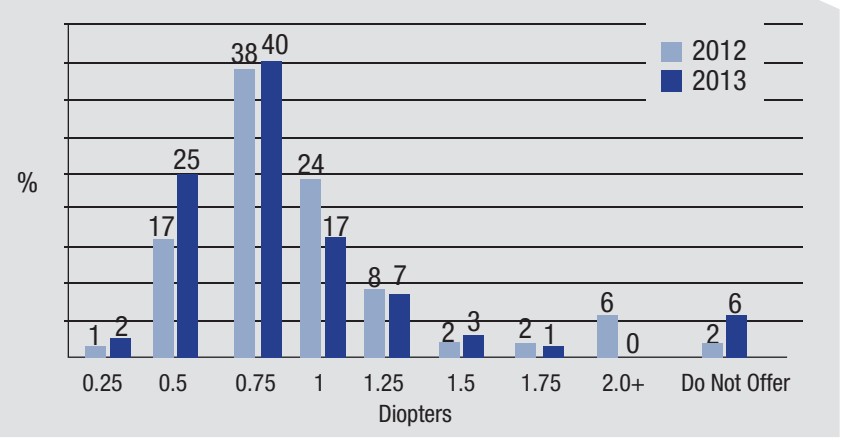
This year's survey of the American members of the International Society of Refractive Surgery gives a glimpse of the practice habits of your fellow surgeons, including data on volumes, astigmatism treatment and ectasia. Among the findings are the revelations that volumes have at least stabilized, rather than continued to drop; many surgeons are attacking astigmatism with more fervor than in the past; and new cases of ectasia are becoming rarer. This year, 144 surgeons, or 13 percent of the sample, responded to the survey.

Procedure Volumes

In terms of overall laser vision correction volume, the number of procedures surgeons say they've done in the past year has remained constant from last year at 451,000 (339,000 LASIK and 112,000 surface ablation); surface ablation has comprised a quarter of all cases on the survey since 2010. "Even though my practice's volume has continued to go down, I'm pleased to see that it hasn't in this cross-section of ISRS members," avers Mobile, Ala., surgeon Richard Duffey, who administers the survey each year with Palm Springs, Calif., ophthalmologist David Leaming. "I think we're still suffering a little bit more in terms of the economy in the Southeast, so it continues to go down here while other areas are stabilizing. And, obviously, the volumes of surgeons in some other areas have gone up, on average, along the way."

Digging into the procedure volumes, in terms of the refractive procedures that surgeons say they perform five or more times per month, toric lenses, presbyopic intraocular lenses and femtosecond cataract lasers (used for refractive purposes) are gaining traction. Half of the surgeons report implanting five or more toric lenses per month; 38 percent say the same for presbyopic IOLs; and 23 percent say they use a femtosecond cataract laser for five or more cases each month. "Those procedures are starting to get some real play in the survey for refractive pro-

Threshold of Astigmatism Correction Pre-Cataract Surgery



Surgeons report the minimum level of astigmatism for which they'll offer a patient the option to correct it before cataract surgery.

This article has no commercial sponsorship.

cedures," observes Dr. Duffey. "It'll be interesting to see what happens with those over time. When you get to the question of procedures that are used for 25 or more cases per month, those three categories drop some, with LASIK and surface ablation having the higher percentages. However, 5 percent of the respondents say they do at least 25 refractive cases per month with the femtosecond cataract laser, which is substantial. These are like the early days of laser vision correction, and I think you'll see great growth in these procedures' numbers over time."

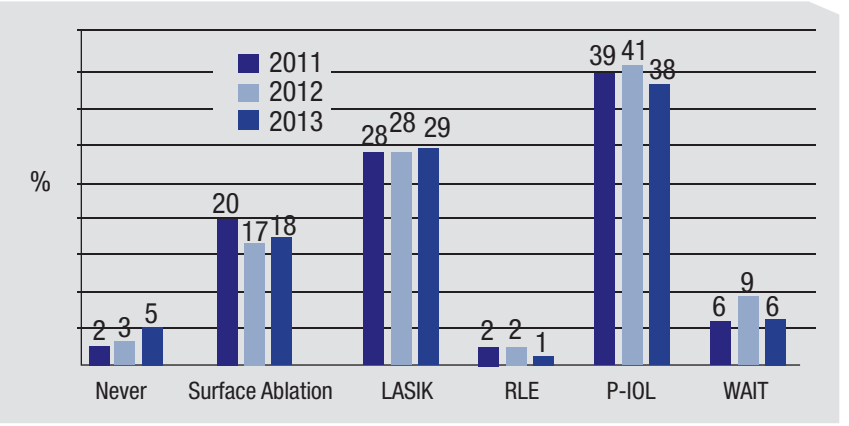
A result that Dr. Duffey is particularly impressed by is the proportion of surgeons who either have refractive surgery done either on themselves or their family members. Forty percent of the surgeons on the survey have had it. In terms of surgery for their family members, refractive surgeons report a percentage that's three times higher than the general population. "If there's any group that knows the most about it, it's the refractive surgeons who do it," says Dr. Duffey.

Treatment Patterns

When it comes to addressing issues such as astigmatism in cataract patients or LASIK flap size, the trend is to try to clean up as much astigmatism as possible and to create thinner LASIK flaps.

In last year's survey, 17 percent of the surgeons said the threshold at which they'd offer astigmatism correction to a cataract patient was 0.5 D. This year, that number has risen to 25 percent. When the astigmatism thresholds are looked at as a group, 67 percent of surgeons will offer to correct astigmatism if it's 0.75 D or more, and 90 percent will offer correction when it reaches 1.25 D. "For the 67 percent who offer it for at least 0.75 D, that's a significant percentage," says Dr. Duffey. "As to why this is, I think we feel more confident in our

Preferred Surgery for a 30-year-old, -10 D Myope



techniques, whether it's AK, a toric lens or a femtosecond astigmatic procedure. We've started to get serious about astigmatism correction when we do cataract surgery, because we're getting very serious about making our patients less dependent on optical aids such as spectacles and contact lenses after their cataract procedure. Also, patients are coming into our offices and asking for it.

"In terms of the procedures used to correct the astigmatism, on the survey if it's less than 1 D, 87 percent of the surgeons will do LRIs and AKs," continues Dr. Duffey. "But, if it's more than that, 75 percent will use a toric IOL. It will be interesting to see what those numbers do as we get more into femtosecond-assisted cataract surgery. For me, I'll correct anything under 2 D with the femtosecond laser—because it's quite effective—before I move onto more expensive toric lens implants. So, it saves the patient some money and I feel I can get close to an equal result."

In terms of how surgeons treat high myopia (-10 D or greater), laser vision correction is chosen by 47 percent, versus 38 percent who say they prefer a phakic IOL. "I'm fascinated by the percentage that will do LVC vs. a phakic lens," says Dr. Duffey. "We all like the idea of staying outside the eye. If I can do it on the surface, I'd much rather do that than place an implant in someone, especially a young patient who's 30 years old. I'm with the LVC surgeons there."

For flap making, surgeons continue to move toward thinner flaps. "I think the biggest thing that stood out is that we used to create 160-µm flaps, but now they are done by only 1 percent of the surgeons on the survey," says Dr. Duffey. "Everyone's doing thinner flaps. I still think that the sweet spot is somewhere in that 100 or so micron range."

One of the possible reasons surgeons are moving toward thinner flaps is to help preserve more corneal strength to ward off ectasia. This fact, as well as the increased use of surface ablation in select patients, may be behind the reason that the survey surgeons aren't reporting new ectasia cases. Forty-seven percent of surgeons report zero cases of ectasia in their career. "What I'm looking for in ectasia responses on the survey is any real spike that's consistent over a two- to three-year period and, frankly, I don't think I'm going to see that," says Dr. Duffey. "This is because everyone is attuned to ectasia risk now with preop testing, and making thinner flaps to leave more residual bed and/or switching to PRK. Knock on wood, I haven't seen a case of ectasia since someone I did before 2001 or 2002. I feel confident that we've got that problem under control." REVIEW

OPHTHALMOLOGY 2014 UPDATE

SAVE THE DATE
February 15-16

CME

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.

Program Chairs:
Don O. Kikkawa, MD
Robert N. Weinreb, MD

Location
Hilton La Jolla Torrey Pines
10950 North Torrey Pines Rd.
La Jolla, CA 92037
Phone: 858-558-1500

Program Times
Saturday, February 15, 2014
7:30am-4:30pm
Reception to follow

Sunday, February 16, 2014
7:30am-12:00pm

Program Chairs:
Don O. Kikkawa, MD
Robert N. Weinreb, MD

Additional Faculty:
Keynote speaker
Gholam Peyman, MD

Featured speakers
Malik Kahook, MD
Eytan Blumenthal, MD
Sameh Mosaed, MD

Invited speakers
Francis Mah, MD
Tommy Korn, MD, FACS
Baruch Kupperman, MD, PhD

UCSD Speakers
Natalie Afshari, MD, FACS
Radha Ayyagari, PhD
Henry Ferreyra, MD
Michael Goldbaum, MD
Jeffrey Goldberg, MD, PhD
David Granet, MD
Weldon Haw, MD
Christopher Heichel, MD
Bobby Korn, MD, PhD
Jeffrey E. Lee, MD
Jonathan Lin, MD, PhD
Felipe Medeiros, MD, PhD
Shira Robbins, MD
Peter Savino, MD
Linda Zangwill, PhD
Kang Zhang, MD, PhD

3 WAYS TO REGISTER
Online: www.revophth.com/Update2014
Email: ReviewMeetings@jobson.com
Call: Lois DiDomenico 800-999-0975

This activity is approved for *AMA PRA Category 1 Credit(s)™*

Jointly Sponsored by

REVIEW® of Ophthalmology IAHB

UC San Diego Shiley Eye Center

Supported by an Independent Educational Grant from

ALLERGAN

Comparing Height Data For Four Topographers

Researchers from the University Medical Center Gronigen, in the Netherlands, performed a cross-sectional study to compare the ability of clinical corneal topographers to describe the shape of the anterior cornea for optical modeling. Unfortunately, test-retest variability hampered a detailed description of the anterior corneal shape at the level of individual subjects, and interdevice variability compromises the exchangeability of the devices.

The anterior corneal shape of healthy subjects was assessed with four topographers (Atlas Placido disk, Galilei dual Scheimpflug, Orbscan scanning slit and Pentacam single Scheimpflug). Exported height data were fit with Zernike polynomials. Mean values with the standard deviation, interdevice variability and test-retest variability were determined for the defocus Z(2,0), astigmatism Z(2,–2) and Z(2,2), coma Z(3,–1) and Z(3,1) and spherical aberration Z(4,0) coefficients for 5.5 mm and 8 mm diameters.

At 5.5 mm, the single Scheimpflug topographer showed the smallest coefficient of repeatability: 0.31 µm for defocus Z(2,0); 0.40 and 0.34 µm for astigmatism Z(2,–2) and Z(2,2), respectively; 0.15 and 0.11 µm for coma Z(3,–1) and Z(3,1), respectively; and 0.08 µm on spherical aberration Z(4,0); the other topographers showed up to 10 times larger coefficients of repeatability. The (unsigned) mean differences were in the range of 0.20 to 1.21 µm for defocus Z(2,0); 0.02 to 0.31 µm and 0.06 to 0.42 µm for astigmatism Z(2,–2) and Z(2,2), respectively; 0.03 to 0.18 µm and 0.03 to 0.35 µm for coma Z(3,–1) and Z(3,1), respectively; and 0 to 0.14 µm for spherical aberration Z(4,0). The Placido-disk topographer and single Scheimpflug topographer data corresponded best. Similar trends were found at 8 mm.

J Cataract Refract Surg 2013; 39:1570-1580.
De Jong T, Sheehan M, Dubbelman M, Koopmans S, et al.

Debridement-scaling: Procedure Reduces Dry-Eye Symptoms

Results of a study from Massachusetts suggests debridement-scaling of the line of Marx and the lower keratinized lid margin provides statistically significant symptom relief of evaporative dry-eye disease and improves meibomian gland function.

Patients symptomatic for and diagnosed with evaporative dry eye who also evidenced anteroplacement and a thickened LOM were alternately and consecutively assigned to the test (n=16) or control (n=12) group. Mean age of the patients was 55.9 ±15 years in the test group vs. 53.7 ±15.3 years in the control. Symptoms were evaluated with the Standard Patient Evaluation of Eye Dryness questionnaire; a minimum of 6/28 was required for admission to the study. Meibomian gland function was also evaluated and the LOM was stained with lissamine green to determine thickness and location.

The stained LOM and the width of the keratinized lower lid margin in the test group were debrided-scaled using a stainless steel, foreign body, golf club spud. All patients were required to abstain from other lid treatments, with exception of artificial tears and warm compresses, and monitored for changes in symptoms and MG function approximately one month later.

There was a significant improvement in symptoms and MG function one month post-debridement-scaling in the test group. The controls evidenced no significant change in either parameter. Patient baseline mean pre-debridement-scaling symptoms were 13.4 ±4.6 (test) vs. 13.9 ±5.5 (control). At one month post-debridement-scaling, symptoms were 10.5 ±3.8 (test; population level statistic <0.0001) vs. 14.3 ±7.5 (control; population level statistic >0.05). The baseline mean pre-debridement-scaling number of functional MGs was 2.6 ±1.3 (test) vs. 2.7 ±1.5 (control) and 3.8 ±1.4 (test; p=0.0007) vs. 2.4 ±1.1 (control; p>0.05) one month later.

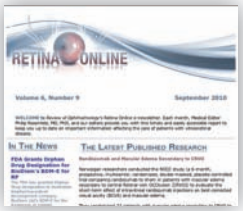
Cornea 2013;32:1554-1557.
Korb D, Blackie C.

REVIEW® of Ophthalmology

ENRICH YOUR PRACTICE

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

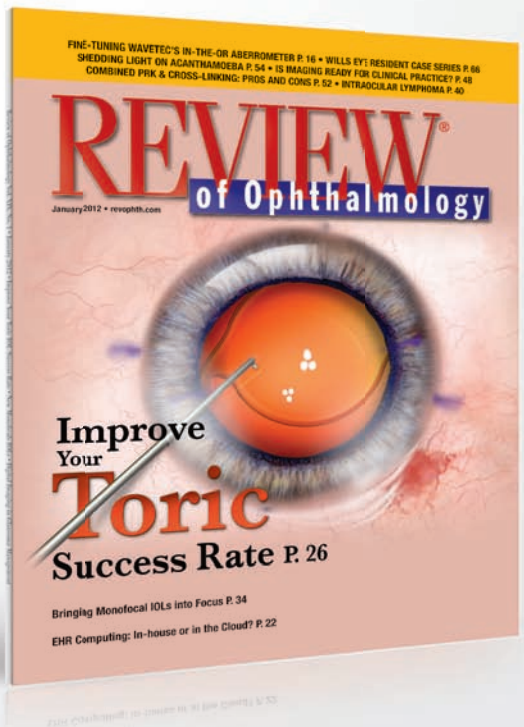
The *Review* Group's *Ophthalmic Product Guide* brings you the latest products and technology on the market. Published every February and July.



The *Review* Group also distributes a variety of supplements, guides and handbooks with your subscription to *Review of Ophthalmology*. These publications are designed to keep you informed on what's new and innovative in the industry on topics ranging from cataract refractive surgery to ocular surface disease.

The *Review* Group also offers valuable Continuing Medical Education sessions in both print and online formats, allowing a convenient way for you to earn CME credits. In addition, we also offer an impressive fleet of free e-newsletters—such as *Review of Ophthalmology Online* and *Review of Ophthalmology's Retina Online*—so you can keep up to date on breaking news and the latest research online.

The Review *Group offers eyecare practitioners quality informational resources dedicated to the growth and education of the profession. The* Review *Group offers a variety of print and online products to enrich your patient care and practice needs.*



The *Review* Group also spearheads meetings and conferences, bringing together experts in the field and providing a forum for practitioners that allows you to educate, and learn from others, in the profession. These meetings cover a broad range of topics in the form of educational or promotional roundtables, CMEs and forums.

www.revophth.com

Jobson Medical Information LLC
***Review* Professional Publications Group**

Prokera Adds Options In Corneal Bandages

Bio-Tissue Inc. announced the introduction of two next-generation Prokera Biologic Corneal Bandage devices.

"We are very pleased to introduce these new Prokera products and expand the therapeutic options in ocular surface regeneration, across the full spectrum of severity, available to ophthalmologists and their patients," said Tom Daniells, chief commercial officer of Bio-Tissue. "The growing Prokera family is the culmination of 15 years of clinical experience in more than 150,000 successful human transplantations, backed by 25 years of government-funded research and over 300 peer-reviewed publications."

Prokera is the only Food and Drug Administration-cleared therapeutic device that reduces inflammation and promotes scar-less healing. New Prokera Slim with Comfort Ring Technology was designed with a slim profile that contours to the ocular surface, moves with the eye and maximizes amniotic membrane contact with the cornea, limbus and limbal stem cells, providing clinical benefits and maximizing patient comfort.

"Prokera Slim is ideal for mild-to-moderate ocular surface conditions," said Preeya K. Gupta, MD, assistant professor of ophthalmology at Duke Eye Center. "This new design facilitates our ability to deliver the benefits of amniotic tissue-mediated active healing to patients with microbial or HSV keratitis, recurrent corneal erosions or corneal abrasions, with a quick, in-office application."

New Prokera Plus incorporates multiple layers of amniotic membrane that make it suitable for therapeutic applications requiring longer biologic action and durability on the ocular surface. It is recommended for use in severe indications such as chemical burns, Stevens Johnson Syndrome and severe corneal ulcers.

Original Prokera is recommended for patients with moderate to severe indications such as neuropathic PED, severe infectious keratitis and post-DSEK for bullous keratopathy.

"Prokera products allow you to match the right therapy to the right patient," said Neel R. Desai, MD, director of cornea and refractive surgery at the Eye Institute of West Florida. "These new additions to the Prokera line are truly innovative technology that provides superior therapeutic outcomes and a more optimal patient experience."

For information, visit biotissue.com.

New CPT Code for Ex-Press Device Levels Payment Rates

Alcon has announced a new Category I *Current Procedural Terminology* Code to be used with the Ex-Press Glaucoma Filtration Device for dates of service on or after January 1, 2014.

The American Medical Association assigned the Category I CPT Code 66183 with the descriptor, "insertion of anterior segment aqueous drainage device, without extraocular reservoir; external approach." It will replace the Category III CPT Code, 0192T, previously used to report implantation of the Ex-Press Glaucoma Filtration Device.

Procedures with Category III CPT Codes are subject to physician payment rates that are assigned individually and at the discretion of each Medicare contractor across the United States. The assignment of the Category I CPT code and the inclusion of 66183 in the national physician fee schedule will provide uniformity to the physician payment rate for the Ex-Press device procedure. At present, the 2014 physician fee schedule is being addressed by Congress and the final Medicare physician payment amount for each CPT was expected to be set by early January.

The Ex-Press Glaucoma Filtration Device is an alternative to conventional trabeculectomy surgery to alleviate intraocular pressure due to glaucoma, while allowing for a quicker recovery. For information, visit alconsurgical.com. REVIEW

This article has no commercial sponsorship.

Equipment and Supplies

Professional Opportunities

Ophthalmology and Subspecialty Opportunities

Geisinger Health System (GHS) is seeking candidates to join the Department of Ophthalmology for the following positions:

- BC/BE fellowship-trained Surgical Retina physician for Geisinger Wyoming Valley (GWV) Medical Center, Wilkes-Barre, Pa.
- BC/BE Cornea/Refractive Surgery Ophthalmologist for Geisinger–Scenery Park, State College, Pa.

About the Surgical Retina Physician Position:

- Join a team consisting of a General Ophthalmologist, Glaucoma specialist and Optometrist
- Established patient base with an experienced support staff and photographer
- Unique technologies include a Fluorescein camera, OCT, HVF and laser
- Teaching opportunities exist with 6 residents
- Research opportunities available

About the Cornea/Refractive Surgery Ophthalmologist Position:

- Opportunity to start up a new practice and develop new programs
- Work with a surgical retina physician and a local Optometry practice
- Enjoy a strong referral base from Geisinger's community practice sites
- Candidate should possess exceptional surgical skills and a dedication to patient care

Discover for yourself why Geisinger has been nationally recognized as a visionary model of integrated healthcare.

For more information, please visit geisinger.org/careers or contact: Autum Ellis, Department of Professional Staffing, at 1-800-845-7112 or amellis1@geisinger.edu.

GEISINGER HEALTH SYSTEM

Products and Services

P.M. MEDICAL BILLING AND CONSULTING

SPECIALIZING IN OPHTHALMOLOGY BILLING & CONSULTING

- *National, full service billing to ophthalmologists*
- *Maximum reimbursement is guaranteed*
- *Staff consists of Ophthalmic techs, expert coders & billers*
- *Increased revenue/low denial rate/complete & unrelenting follow up*

We specialize in old, outstanding AR, Practice Management & Credentialing

Contact us at:
pmmedbill@aol.com
or call us toll-free at:
1-888-PM-BILLING
for a free in-office consultation
WWW.PMOPHTHALMOLOGYBILLING.COM

Practice Consulting

FOCUSED MEDICAL BILLING
A FULL SERVICE MEDICAL BILLING FIRM SPECIALIZING IN OPHTHALMOLOGY

Focused Medical Billing is a full service medical billing & practice consulting firm based out of New York servicing ONLY Ophthalmology practices.

We chose the name Focused Medical Billing because we wanted our clients to be certain of what they are getting with our firm. Our focus each and every day is to maximize our client's revenue by utilizing over a decade of experience and expertise in Billing, Coding, A/R Recovery, Forensic Billing, Practice Management and Consulting.

- Outsourced Billing lowers your overhead and maximizes revenue
- Full Service Billers specializing ONLY in Ophthalmology practices

Services include:
Billing | A/R Clean-Up | Practice Establishment
Practice Consulting & Management | Expert coding guarantees maximum reimbursement and minimal denials

"Free, no obligation consultation"

- 14+ years experience in Ophthalmology billing, practice management & consulting
- No long term commitment or contract required.
- Your satisfaction with our service will make you a client for life.
- Electronic Claims Submission - 48 Hour Claim Submission Guarantee!
- 100% HIPAA Compliant

1-855-EYE-BILL
focusedmedicalbilling@yahoo.com • www.focusedmedicalbilling.com

Practice For Sale

Practice Consultants
Practice Sales • Appraisals • Consulting
www.PracticeConsultants.com

PRACTICES FOR SALE NATIONWIDE

Visit us on the Web or call us to learn more about our company and the practices we have available.

info@practiceconsultants.com
800-576-6935

www.practiceconsultants.com

PRACTICE FOR SALE

Thriving comprehensive ophthalmology general practice in central PA. Seller is board certified and willing to help the purchaser transition. This is a turnkey opportunity available immediately or anytime in the next year or so.

Please respond to:
eyepractice@verizon.net

For classified advertising
call 1-888-498-1460
or e-mail us at sales@kerhgroup.com

kerh group

New-onset 'crossed-eyes' are blamed for a minor accident, but the driver's other problems lead to a request for evaluation.

Charles Calvo, MD

Presentation

The Wills Eye Hospital Neuro-ophthalmology service was consulted to evaluate a 55-year-old male inpatient with the complaint of new-onset "crossed eyes." The patient was driving his car in a convenience store parking lot and crashed his vehicle into a parked car at a speed of less than 5 mph. When police arrived at the scene, they noted the man to be confused as well as unsteady on his feet, and he was transported to a local hospital. The patient's relatives were called to the hospital and noted his new-onset "crossed eyes."

The patient was a poor historian but was able to admit to double vision. Further details about the diplopia could not be elicited. He denied a decrease in visual acuity. Other than his difficulty ambulating, review of systems could not reliably be obtained due to his altered mental status.

Medical History

Past medical history was significant for alcohol abuse and subdural hematoma requiring craniotomy after a fall four months earlier. The patient took no chronic medications. Family history was unremarkable.

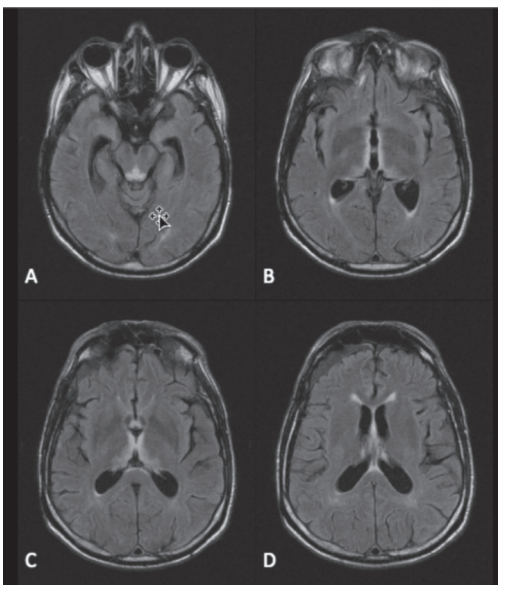
Examination

The patient was afebrile with normal vital signs. He was disheveled in appearance, in no acute distress, but alert and oriented to self only. Uncorrected visual acuity was 20/50 in both eyes with near card; no afferent pupillary defect was detected, and color plates were full.

The patient demonstrated 15 prism diopters of esotropia in primary gaze at distance. Ductions in the right eye were full other than 70 percent abduction and 90 percent adduction. Ductions in the left eye were full other than 70 percent abduction and 90 percent adduction. Horizontal jerk nystagmus in left and right gaze and upbeating, torsional nystagmus in upgaze were noted in both eyes.

Anterior segment examination was only notable for 2+ nuclear sclerosis. Dilated fundus exam was within normal limits with no optic disc edema.

An urgent CT scan of the head was obtained in the emergency department, demonstrating a stable right frontal subdural hygroma and no new intracranial hemorrhage. Magnetic resonance imaging was then performed of the brain *(See Figure 1)*.



Figfure 1. Abnormal MRI FLAIR signal surrounding: A) the aqueduct of Sylvius and within the region of the trochlear nerve nucleus; B) periventricular grey matter of the third ventricle; and C) & D), the medial thalamus.

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

Diagnosis, Workup and Treatment

A broad differential diagnosis for new-onset motility abnormalities, nystagmus, altered mental status and ataxia was considered. Possible etiologies included metabolic abnormalities, intoxication, stroke, encephalitis, meningitis and demyelinating disease.

The brain MRI showed numerous, symmetric, abnormal T2 FLAIR signal intensities within the bilateral thalami, symmetric regions surrounding the third ventricle, the aqueduct of Sylvius and within the region of the trochlear nerve nucleus. From the clinical history and exam, these symmetric T2 signal intensities were highly suggestive of Wernicke's encephalopathy.

Complete blood count, chemistry panel and coagulation studies were normal other than hemoglobin of 12.5 g/dL. Blood ethanol level and urine toxicology were normal, which ruled out acute intoxication. Serum vitamin B12 was also within normal limits. Given the patient's history of alcohol abuse, a serum B1 (thiamine) level was obtained and found to be 1.9 µg/dL (normal 2.5 to 7.5µg/dL).

The patient was started on parenteral thiamine in addition to nutritional support and measures to prevent alcohol withdrawal. Improvement in ophthalmoplegia and nystagmus was seen within three days of treatment and improvement in ataxia within two weeks. The delirium began to resolve within three days of treatment, but the patient continued to have significant memory difficulties. At three months follow-up, there was some further improvement, but the patient remains in a long-term care facility.

Discussion

Wernicke's encephalopathy is a life-threatening neurological disease caused by a deficiency in vitamin B1 (thiamine). It is characterized by the triad of ophthalmoplegia, altered mental status and ataxia, but this triad is seen in only 16 percent of patients.[1,2] Within approximately two to three weeks of deficient thiamine intake or absorption, brain lesions develop in regions with high thiamine content and turnover.[3,4]

While classically associated with chronic alcohol abuse, Wernicke's encephalopathy may also be secondary to malnutrition, gastrointestinal surgical procedures, chronic vomiting or diarrhea and complications related to systemic diseases like AIDS.[7] The condition is a medical emergency as it carries an estimated mortality of 17 percent.[5] Eighty-five percent of survivors develop a memory disorder or Korsakoff syndrome, and 25 percent require long-term institutionalization.[5]

Twenty-nine percent of patients with Wernicke's encephalopathy show some ocular abnormality. Findings can include nystagmus, unilateral or bilateral palsy of any extraocular muscles and conjugate-gaze palsies. Ophthalmoplegia results from insults to the pontine tegmentum, abducens or oculomotor nuclei.[1] Optic disc edema and retinal hemorrhages have also been reported in patients presenting with Wernicke's encephalopathy.[6]

Magnetic resonance imaging is currently regarded as the most valuable modality to diagnose Wernicke's encephalopathy. Despite a sensitivity of only 53 percent, a specificity of 93 percent makes MRI a valuable tool if typical findings are present. These findings include a bilateral increased T2 signal in the hypothalamus, mammillary bodies, paraventricular regions of the thalamus, periaqueductal grey matter, the floor of the fourth ventricle and midline cerebellum.[7]

Ultimately, improvement of neurological deficits after thiamine administration is the best method of confirming the diagnosis. Ocular abnormalities usually improve within days to weeks but ataxia and global confusion may require at least three months to significantly improve.[1,2] Blood thiamine concentrations and red blood cell transketolase activity can also be helpful in supporting clinical suspicion; however, they may be abnormal in patients who do not have encephalopathy.[8,9]

The differential diagnosis of Wernicke's encephalopathy includes encephalitis; paramedian thalamic infarction; Miller-Fisher variant of Guillain-Barre syndrome; multiple sclerosis; primary cerebral lymphoma; Behçet's disease; and variant Creutzfeldt-Jakob disease.[10] A carefully obtained history evaluating risk factors for Wernicke's encephalopathy may be the most beneficial tool for the consulting ophthalmologist. REVIEW

The author thanks Mark Moster, MD, Wills Eye Hospital Neuro-ophthalmology Service, for his time and assistance in preparing this case report.

1. Victor M. The Wernicke-Korsakoff syndrome, Handbook of Clinical Neurology, vol 28, part II. Amsterdam: North-Holland Publishing Co., 1976:243–270.
2. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatry 1986;49:341-345
3. Manzo L, Locatelli C, Candura SM, Costa LG. Nutrition and alcohol neurotoxicity. Neurotoxicology 1994;15:555-565.
4. Schenker S, et al. Hepatic and Wernicke's encephalopathies: Current concepts of pathogenesis. Am J Clin Nutr 1980;33:2719-2726.
5. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome: A clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp Neurol Ser 1971;7:1-206.
6. Cooke CA, et al. An atypical presentation of Wernicke's encephalopathy in an 11-year-old child. Eye 2006;20:1418-1420.
7. Antunez E, et al. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. Am J Roentgenol 1998;171:1131-1137.
8. Baker H, et al. A method for assaying thiamine status in man and animals. Am J Clin Nutr 1964;14:197-201.
9. Dreyfus PM. Clinical application of blood transketolase determinations. N Engl J Med 1962;267:596-598.
10. Brechtelsbauer DL. Cytomegalovirus encephalitis and primary cerebral lymphoma mimicking Wernicke's encephalopathy. Neuroradiology 1997;39:19-22.

(continued from page 25)

your OR microscope or your femtosecond laser; the digital marker portion then provides a digital overlay on the eye showing exactly where the orientation of your LRI/AK incision or toric IOL position should be.

"This is going to be a paradigm shift, in terms of not having to manually mark the patient preoperatively or intraoperatively to know where the toric IOL should align," he adds. "I think it's going to be a big improvement, simplifying and automating the process as well as eliminating the risk of transposition and transcription errors."

> *"In general, toric lenses are my favorite lenses. To me, they eclipse multifocal IOLs as a valuable adjunct to my cataract practice."*
> *—Douglas D. Koch, MD*

In the meantime, Dr. Mamalis notes that there are plenty of new toric lenses that simply haven't made it into the United States. "Around the world there are toric options too numerous to count," he says. "Most are not approved in the United States. There are torics made of both hydrophobic and hydrophilic acrylic materials, and some that are made to go into the sulcus as a piggyback lens. We've tried those in our laboratory; they allow you to correct astigmatism without corneal or lenticular surgery. I think they're a great option, but that's a niche market, and the cost of getting approved by the FDA is very high. Also, in Europe, Rayner will custom-make an IOL for your patient. That could potentially save the surgeon from having to combine a toric IOL with arcuate incisions in the cornea or LASIK surgery on the cornea."

With the technology advancing—and more toric IOL approvals inevitable—it seems clear that these lenses are likely to become an ever-larger part of the cataract surgeon's armamentarium. "This is an excellent technology, and I think it will continue to be part of our armamentarium to treat astigmatism, even with the availability of femtosecond lasers to make corneal incisions," says Dr. Mamalis. "I don't think this is going to go away."

Dr. Koch agrees. "In general, toric lenses are my favorite lenses," he says. "To me, they eclipse multifocal IOLs as a valuable adjunct to my cataract practice." REVIEW

1. Koch DD, Ali SF, Weikert MP, et al. Contribution of posterior corneal astigmatism to total corneal astigmatism. J Cataract Refract Surg 2012;38:12:2080-2087.

LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

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

ADVERSE REACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

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

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

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

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

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

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

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

OVERDOSAGE

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

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

NONCLINICAL TOXICOLOGY

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

APC70EN12 based on 71807US13.

Rx only

ALLERGAN®

Tonometry Done Right

KAT
Keeler quality.

Pulsair Desktop
Smallest footprint and simple to use!

Purchase a Pulsair Desktop by March 31, 2014 and get a $1,300 Instant Rebate!

Intellipuff
The standard for hand held mobility.

Buy Online!
keelerusa.com

Keeler
OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

Monotherapy Maintained.

Proven IOP reduction[1]

•

Established tolerability with
low discontinuation rate[2]

On Your Terms.

Broad preferred coverage[3]

•

Comprehensive patient support

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

Important Safety Information

Warnings and Precautions: LUMIGAN® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® 0.01% should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. LUMIGAN® 0.01% has not been studied to treat types of glaucoma other than open-angle glaucoma. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® 0.01% was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

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

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

Allergan at your service

1. LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol.* 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of November 2013.