REVIEW® of Ophthalmology

December 2015

reviewofophthalmology.com

THE DIGITAL FRONTIER:

Social Media and Patient Care

INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Make the move to ILUVIEN and provide sustained, submicrogram levels of fluocinolone acetonide (FAc) for 36 months from a single intravitreal implant.[1]

Primary month-24 endpoint met. Significantly more patients treated with ILUVIEN achieved ≥15-letter improvement from baseline.[1]

The most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of >10 mmHg (ILUVIEN 34%; sham 10%).[1]

Nonbioerodable, implant designed to deliver submicrogram levels of steroid.[1]

Important Safety Information

Contraindications

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the

1.ILUVIEN® [package insert]. Alpharetta, GA: Alimera Sciences, Inc.; 2014.

NEW!

Permanent **J-code** has been issued for ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg

Effective January 1 2016

In the fight

against DME...

SHIFT to a

multiyear approach

establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

- The most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of >10 mmHg (ILUVIEN 34%; sham 10%).

ILUVIEN®

(fluocinolone acetonide intravitreal implant) 0.19mg

Learn more at ILUVIEN.com

Please see brief summary of full Prescribing Information on following page.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

Ocular or Periocular Infections: ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Glaucoma: ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Hypersensitivity: ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

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

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

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

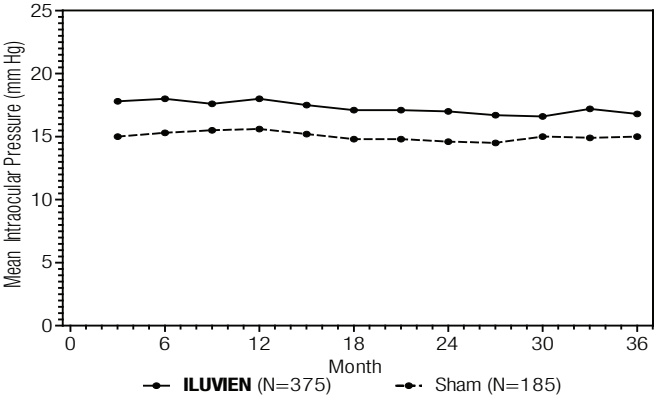


Figure 1: Mean IOP during the study

Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Postmarketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, 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 **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.

There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.

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

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

Manufactured for:
Alimera Sciences, Inc. • 6120 Windward Parkway
Alpharetta, GA 30005 • Patented. See: www.alimerasciences.com

ALIMERA SCIENCES

REVIEW NEWS
Volume XXII • No. 12 • December 2015

L-dopa May Hold Key to Prevention, Delay of AMD

A University of Arizona-led study on age-related macular degeneration likely will lead to a way to delay or prevent the disease, researchers say.

The study, led by co-principal investigator Brian S. McKay, associate professor of ophthalmology and vision science and cellular and molecular medicine at the UA College of Medicine-Tucson, found that patients who take levodopa, or l-dopa, a common treatment for Parkinson's disease, appear far less likely to develop macular degeneration. And if they do develop the disease, it is significantly later in life.

L-dopa is a naturally occurring molecule that is made in pigmented human tissue, including the iris, and has a role in maintaining a healthy macula. A synthesized form of l-dopa is used to treat Parkinson's and movement disorders.

"It is likely that this will lead to a way to prevent AMD, and it may also lead to treatment for macular degeneration in the future," Dr. McKay said. "It may also help with other eye diseases characterized by retinal degeneration, such as retinitis pigmentosa." The research was published online Nov. 4 in the *American Journal of Medicine*.

"Research points to this as a pathway to regulate and prevent this most common cause of blindness in adults," said study co-principal investigator Murray Brilliant, PhD, director of the Marshfield Clinic Research Foundation Center for Human Genetics in Marshfield, Wisc. "Imagine telling patients we potentially have medication that will allow them to see and continue enjoying life, their family and perform everyday activities as they age. That is very powerful."

Dr. Paul A. Sieving, director of the National Eye Institute, a branch of the National Institutes of Health, said the research "suggests an intriguing link between patients taking l-dopa and a lower incidence and delayed onset of AMD. Showing that l-dopa causes this protective effect will require further investigation, but if confirmed, could lead to new drugs or combination therapies for AMD that target dopa-responsive cells in the retina."

Dr. McKay pursued this research after he discovered that the support tissue for the retina expressed a receptor for l-dopa, and that this signaling pathway fostered retinal survival. He and Dr. Brilliant, who previously was with the UA, hypothesized that those taking l-dopa may be protected from AMD.

To answer this question they analyzed the health records of 37,000 Marshfield Clinic patients to determine who had macular degeneration, who took l-dopa, or both. Dr. Brilliant found that patients who began taking l-dopa before they developed macular degeneration were diagnosed with the eye disease eight years later than those who had never taken l-dopa. They also noted that there were many fewer AMD patients in the group that were prescribed l-dopa.

The next phase of the research involved analysis of a much larger, insurance-industry database of medical records on 87 million patients. The same connection between l-dopa and macular degeneration held. Further, with this enormous dataset, they were able to show that l-dopa both prevented and delayed wet AMD, which is far less common than dry AMD but is responsible for about 90 percent of AMD-caused blindness.

A clinical trial to further validate these research findings will be the next step of the research.

Cataract-Staving Drop Identified

A chemical that could potentially be used in eye drops to reverse cataracts has been identified by a team of scientists from UC San Francisco, the University of Michigan and Washington University in St. Louis.

Identified as a "priority eye disease" by the World Health Organization, cataracts affect more than 20 million people worldwide. Most individuals blinded by severe cataracts in developing countries go untreated.

Reported November 5, 2015 in *Science*, the newly identified compound is the first that is soluble enough to potentially form the basis of a practical eye-drop medication for cataracts.

As is seen in neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, a

Reimbursement Update Course for Ophthalmology and Optometry

TOPICS THAT WILL BE COVERED:

- Coding Eye Exams With Corcoran's Office Visit Matrix: Better & Faster
- Resolving ICD-10 Problems After Inauguration
- Responding To A Payer's Chart Audit and Criticism
- What's New in the Medicare Program?
- Getting Modifiers Right: Fast-paced Interactive Challenge
- Update On Medicare's Incentive Programs (PQRS, VBPM, MU)
- Utilization Benchmarking: Identifying Underused And Overused Services

REGISTER TODAY!

Space is limited

KEVIN J. CORCORAN
COE, CPC, CPMA, FNAO
President
Over 39 years Ophthalmic experience

MARY PAT JOHNSON
COMT, COE, CPC, CPMA
Senior Consultant
Over 30 years Ophthalmic experience

TRICIA L. KOLB
COT, CPC, OSC
Associate Consultant
Over 20 years Ophthalmic experience

PAUL M. LARSON
MMSC, MBA, COMT, COE, CPC, CPMA
Senior Consultant
Over 39 years Ophthalmic experience

KIRK A. MACK
COMT, COE, CPC, CPMA
Senior Consultant
Over 25 years Ophthalmic experience

DONNA M. MCCUNE
CCS-P, COE, CPMA
Vice President
Over 29 years Ophthalmic experience

Course approved for 8.0 Continuing Education Credits for **AAPC, COPE, NBCOE and JCAHPO**

Corcoran Consulting Group

www.corcoranccg.com **1.800.399.6565**

hallmark of diseases of aging is the misfolding and clumping together of crucial proteins. In the case of cataracts, the affected proteins are known as crystallins.

Crystallins are the major component of fiber cells, which form the eyes' lenses, and the unique properties of these cells make them particularly susceptible to damage, said Jason Gestwicki, PhD, an associate professor of pharmaceutical chemistry at UCSF and co-senior author of a paper on the new research.

"Shortly after you're born, all the fiber cells in the eye lose the ability to make new proteins, or to discard old proteins," said Dr. Gestwicki. "So the crystallins you have in your eye as an adult are the same as those you're born with."

In order for our lenses to function well, this permanent, finite reservoir of crystallins must maintain both the transparency of fiber cells and their flexibility. The crystallins accomplish these duties with the help of aptly named proteins known as chaperones, which act "kind of like antifreeze," Dr. Gestwicki said, "keeping crystallins soluble in a delicate equilibrium that's in place for decades and decades."

This state-of-affairs is delicate because pathological, clumped-together configurations of crystallins are far more stable than properly folded, healthy forms, and fiber-cell chaperones must continually resist the strong tendency of crystallins to clump. A similar process underlies other disorders related to aging, such as Alzheimer's disease, but in each of these diseases the specific protein that clumps together and the place in the body that clumping occurs is different. In all cases, these clumped-together proteins are called amyloids.

In the new study, led by Leah N. Makley, PhD, and Kathryn McMenimen, PhD, the scientific team exploited a crucial difference between

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

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

Senior 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. — (845) 267-3065
E-mail:
rhsubs@halldata.com
Website: www.reviewofophthalmology.com

jmi BPA

REVIEW News

properly folded crystallins and their amyloid forms: Put simply, amyloids are harder to melt.

The research group used high-throughput differential scanning fluorimetry, or HT-DSF, in which proteins emit light when they reach their melting point. At the U-M Life Sciences Institute's Center for Chemical Genomics, the team used HT-DSF to apply heat to amyloids while applying thousands of chemical compounds.

Because the melting point of amyloids is higher than that of normal crystallins, the team focused on finding chemicals that that lowered the melting point of crystallin amyloids to the normal, healthy range.

The group began with 2,450 compounds, eventually zeroing in on 12 that are members of a chemical class known as sterols. One of these, known as lanosterol, was shown to reverse cataracts in a June 2015 paper in *Nature*, but because lanosterol has limited solubility the group who published that study had to inject the compound into the eye for it to exert its effects.

Using lanosterol and other sterols as a clue, Dr. Gestwicki and his group assembled and tested 32 additional sterols, and eventually settled on one, which they call "compound 29," as the most likely candidate that would be sufficiently soluble to be used in cataract-dissolving eye drops.

In laboratory dish tests, the team confirmed that compound 29 significantly stabilized crystallins and prevented them from forming amyloids. They also found that compound 29 dissolved amyloids that had already formed. Through these experiments, said Dr. Gestwicki, "we are starting to understand the mechanism in detail. We know where compound 29 binds, and we are beginning to know exactly what it's doing."

The team next tested compound 29 in an eye-drop formulation in mice carrying mutations that make them predisposed to cataracts. In experiments conducted with Usha P. Andley, PhD, professor of ophthalmology and visual sciences at WUSTL School of Medicine, they found that the drops partially restored transparency to mouse lenses affected by cataracts, as measured by a slit-lamp test of the sort used by ophthalmologists to measure cataracts in humans.

Similar results were seen when compound 29 eye drops were applied in mice that naturally developed age-related cataracts, and also when the compound was applied to human lens tissue affected by cataracts that had been removed during surgery.

Dr. Gestwicki cautions that slit-lamp measures of lens transparency used in the research are not a direct measure of visual acuity, and that only clinical trials in humans can establish the value of compound 29 as a cataract treatment. He has licensed the compound from U-M, however, and Dr. Makley, a former graduate student and postdoctoral fellow in the Gestwicki laboratory, is founder and chief scientific officer of ViewPoint Therapeutics, a company that is actively developing compound 29 for human use.

Dogs are also prone to developing cataracts. Half of all dogs have cataracts by nine years of age, and virtually all dogs develop them later in life. An effective eye-drop medication could potentially benefit about 70 million affected pet dogs in the United States.

"If you look at an electron micrograph at the protein aggregates that cause cataracts, you'd be hard-pressed to tell them apart from those that cause Alzheimer's, Parkinson's or Huntington's diseases," Dr. Gestwicki said. "By studying cataracts we've been able to benchmark our technologies and to show by proof-of-concept that these technologies could also be used in nervous system diseases, to lead us all the way from the first idea to a drug we can test in clinical trials." REVIEW

REVIEW Editorial Board

Contributors

CHIEF MEDICAL EDITOR
Mark H. Blecher, MD

BOTTOM LINE
Dennis D. Sheppard, MD

CONTACT LENSES
Penny Asbell, MD

CORNEA / ANTERIOR SEGMENT
Thomas John, MD

GLAUCOMA MANAGEMENT
Peter Netland, MD, PHD
Kuldev Singh, MD

MASTERS OF SURGERY
Taliva D. Martin, MD
Sara J. Haug, MD, PhD

PEDIATRIC PATIENT
Christopher M. Fecarotta, MD

PLASTIC POINTERS
Ann P. Murchison, MD, MPH

WILLS RESIDENT CASE SERIES
Alia Duranni, MD

REFRACTIVE SURGERY
Arturo S. Chayet, MD

RETINAL INSIDER
Carl Regillo, MD, FACS
Emmett T. Cunningham Jr., MD, PHD, MPH

TECHNOLOGY UPDATE
Steven T. Charles, MD
Michael Colvard, MD

THERAPEUTIC TOPICS
Mark Abelson, MD

Advisory Board

PENNY A. ASBELL, MD, NEW YORK CITY
WILLIAM I. BOND, MD, PEKIN, ILL.
ALAN N. CARLSON, MD, DURHAM, N.C.
Y. RALPH CHU, MD, EDINA, MINN.
ADAM J. COHEN, MD, DOWNERS GROVE, ILL.
UDAY DEVGAN, MD, FACS, LOS ANGELES
ERIC DONNENFELD, MD, ROCKVILLE CENTRE, N.Y.
DANIEL S. DURRIE, MD, KANSAS CITY, MO.
ROBERT EPSTEIN, MD, MCHENRY, ILL.
ROBERT D. FECHTNER, MD, NEWARK, N.J.
WILLIAM J. FISHKIND, MD, TUCSON, ARIZ.
JAMES P. GILLS, MD, TARPON SPRINGS, FLA.
HARRY GRABOW, MD, SARASOTA, FLA.
DOUGLAS K. GRAYSON, MD, NEW YORK CITY
R. BRUCE GRENE, MD, WICHITA, KAN.
THOMAS S. HARBIN, MD, MBA, ATLANTA
DAVID R. HARDTEN, MD, MINNEAPOLIS
KENNETH J. HOFFER, MD, SANTA MONICA, CALIF.
JACK T. HOLLADAY, MD, MSEE, HOUSTON
JOHN D. HUNKELER, MD, KANSAS CITY, MO.
THOMAS JOHN, MD, TINLEY PARK, ILL.
ROBERT M. KERSHNER, MD, MS, FACS, BOSTON
GUY M. KEZIRIAN, MD, PARADISE VALLEY, ARIZ.
TERRY KIM, MD, DURHAM, N.C.
TOMMY KORN, MD, SAN DIEGO
DAVID A. LEE, MD, HOUSTON
FRANCIS S. MAH, MD, PITTSBURGH
NICK MAMALIS, MD, SALT LAKE CITY
WILLIAM G. MARTIN, MD, OREGON, OHIO
MIKE S. MCFARLAND, MD, PINE BLUFF, ARK.
JEFFREY B. MORRIS, MD, MPH, ENCINITAS, CALIF.
MARLENE R. MOSTER, MD, PHILADELPHIA
ROBERT J. NOECKER, MD, FAIRFIELD, CONN.
ROBERT OSHER, MD, CINCINNATI
MARK PACKER, MD, WEST PALM BEACH, FLA.
STEPHEN PASCUCCI, MD, BONITA SPRINGS, FLA.
PAUL PENDER, MD, BEDFORD, N.H.
CHRISTOPHER J. RAPUANO, MD, PHILADELPHIA
AUGUST READER III, MD, SAN FRANCISCO
TONY REALINI, MD, MORGANTOWN, W.V.
KENNETH J. ROSENTHAL, MD, GREAT NECK, N.Y.
ERIC ROTHCHILD, MD, DELRAY BEACH, FLA.
SHERI ROWEN, MD, BALTIMORE
JAMES J. SALZ, MD, LOS ANGELES
INGRID U. SCOTT, MD, MPH, HERSHEY, PA.
JOEL SCHUMAN, MD, PITTSBURGH
GAURAV SHAH, MD, ST. LOUIS
DAVID R. STAGER JR., MD, DALLAS
KARL STONECIPHER, MD, GREENSBORO, N.C.
JAMES C. TSAI, MD, NEW HAVEN, CONN.
VANCE THOMPSON, MD, SIOUX FALLS, S.D.
FARRELL C. TYSON, MD, CAPE CORAL, FLA.
R. BRUCE WALLACE III, MD, ALEXANDRIA, LA.
ROBERT G. WILEY, MD, CLEVELAND
FRANK WEINSTOCK, MD, CANTON, OHIO
JACQUELINE M.S. WINTERKORN, MD, PHD, NEW YORK CITY

REVIEW of Ophthalmology

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
PUBLISHER
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

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

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

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 71, Congers, NY 10929-0071. 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 (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

D-KAT Digital

The first FDA 510(k) digital applanation tonometer

40H Slit Lamp

The next generation slit lamp featuring advanced Keeler optics

Vantage Plus Wireless

The world's best selling binocular indirect ophthalmoscope

MULTIPLY YOUR SAVINGS

BUY MORE SAVE MORE

Keeler's 40H Slit Lamp is quickly gaining the reputation as a world class device.

Featuring Keeler's famous optics, 6 to 40x magnification, LED Illumination in a beautifully crafted, thoughtful design, giving you the functionality and performance you want, need and expect from a Keeler Slit Lamp.

BUY 1 / GET 1
Purchase a Keeler 40 H Slit Lamp and you'll receive a FREE Keeler D-KAT Digital

BUY 2 / GET 2
Purchase 2 Keeler 40H Lamps and you'll receive 2 FREE Keeler D-KAT Digitals

BUY 3 / GET 3 + 1
Purchase 3 Keeler 40H Slit Lamps and you'll receive 3 FREE Keeler D-KAT Digitals + a FREE Keeler Vantage Plus BIO

Outfit your offices with Keeler 40H Slit Lamps before December 31, 2015 and take advantage of these great offers!

Offer expires December 31, 2015. No other Keeler offer can be combined.

Keeler OPTICS

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

The first and only FDA-approved product that combines miosis prevention and post-op ocular pain reduction in one[1]

OMIDRIA® (phenylephrine and ketorolac injection) 1% / 0.3% IS COVERED FOR MORE CATARACT SURGERY PATIENTS THAN YOU THINK

Introducing

OMIDRIAssure™

COVERAGE WITH CONFIDENCE

IMPORTANT SAFETY INFORMATION

OMIDRIA® must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatories (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

Because every patient deserves access to OMIDRIA...

Enroll your next cataract surgery patient in OMIDRIAssure now!

Now you can provide the benefits of OMIDRIA— without worrying about coverage and reimbursement

LIVE ASSISTANCE
INFORMATION HOTLINE

Personalized help with reimbursement services related to OMIDRIA

"WE PAY THE DIFFERENCE"
COMMERCIAL REIMBURSEMENT PROGRAM*

Assistance for patients with insufficient commercial insurance

"EQUAL ACCESS"
PATIENT ASSISTANCE PROGRAM

Assistance for financially eligible uninsured or government-insured patients

Talk to your Omeros Representative today or call **1-877-OMIDRIA** (1-877-664-3742) to request a Patient Enrollment Form, or visit **www.OMIDRIAssure.com**

*Omeros will pay your facility, on behalf of your patient, the difference between your facility's acquisition cost for OMIDRIA and the amount covered by your patient's insurance, less a $30 patient responsibility.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015.

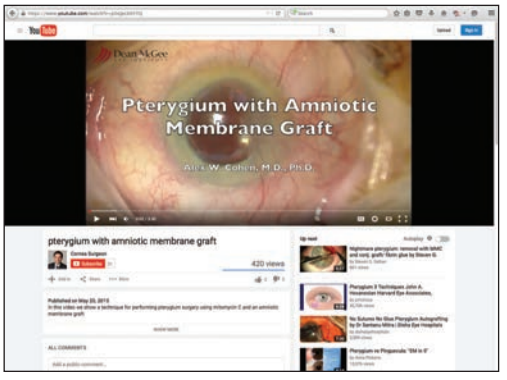
OMIDRIA®
(phenylephrine and ketorolac injection) 1% / 0.3%

REVIEW® of Ophthalmology

December 2015 • Volume XXII No. 12 | reviewofophthalmology.com

Departments

Cover Focus



Cover image: ©iStock.com/JobsonHealthcare

CVS Essential

The Lombart Visual Acuity System

Simple
and Affordable.

The CVS Essential includes:

- Monitor
- HDMI Device with Acuity Software Program
- Luminous RF Remote
- Wall Mounting Bracket with Swivel

Only
$1,695

2.4G RF Remote

Luminous Keypad

Acuity Systems don't have to be complicated. The CVS Essential proves they can be simple and affordable.

There are many visual acuity systems available in the market today. Many of these have features that often go unused and require extensive knowledge of their complicated remote controls to access them.

The ***Lombart CVS Essential*** unit was developed with the idea that an acuity system should be easy to operate, while still including the standard acuity charts commonly used in refraction. The ***CVS Essential*** provides quick access to charts and features, ease of installation and most of all … is priced right!

The ***CVS Essential*** provides standard optotypes in a full range of Snellen Ratios. The remote control is easy to understand with quick access to all optotypes and smooth transitions when adjusting chart sizes. It offers a direct button for chart randomization as well as for Red/Green duochrome testing on all optotypes.

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
www.lombartinstrument.com
lombart@lombartinstrument.com

Sales and Service Centers Coast to Coast

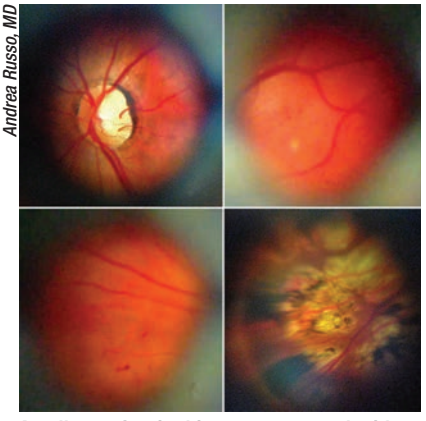
ATLANTA • BALTIMORE/WASHINGTON D.C. • BOSTON • BOYNTON BEACH/MIAMI • BRADENTON • CHARLOTTE • CHICAGO • CINCINNATI • DALLAS • DENVER • DETROIT • GREENSBORO • HOUSTON
JACKSON • KANSAS CITY • KNOXVILLE • LOS ANGELES • MILWAUKEE • MINNEAPOLIS • NEW JERSEY/NEW YORK/PENNSYLVANIA • NORFOLK • PORTLAND • SAN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


Retinal Imaging On the Cheap

Portable, smartphone-based imaging solutions that allow the diagnostician to hit the road without breaking the bank.

Walter Bethke, Managing Editor

If your practice's technology budget is tapped out but you find yourself in need of a portable retinal imager to use for hospital rounds, nursing home visits or pediatric patients, you're in luck: There are a couple of new phone adapters and apps that allow you to document retinal findings for under $500. Here's a look at how these devices work, as well as their benefits and limitations.



Andrea Russo, MD

A collage of retinal images captured with the new D-Eye system.

D-Eye

The D-Eye Portable Retinal Imaging System (D-Eye, Padova, Italy) is a lens assembly that magnetically attaches to a late-model Apple iPhone or Samsung Galaxy.

Andrea Russo, MD, a practicing ophthalmologist and PhD candidate at Italy's University of Brescia, invented the D-Eye. "About 20 years ago, they joined digital cameras with PCs in order to record the view of the retina in our offices," Dr. Russo says. "Now, we have the smartphone, which is a computer in your pocket. When I finished my residency program, I decided to use a few lenses to create the D-Eye project. Essentially, the D-Eye is a direct ophthalmoscope for viewing the retina using just a smartphone held close to the patient's eye."

The D-Eye uses a -10-D lens to compensate for any myopia a patient may have. The other components are a beam splitter and a mirror. "The mirror is used to reflect the light coming from the LED inside the smartphone and the beam splitter is for conveying the light into the patient's eye," Dr. Russo explains. "We also use a couple of polarizing filters that are important for reducing the glare from the cornea, or the Purkinje reflection. For a hyperopic patient, we use the camera's internal autofocus system to compensate for the hyperopia." Since a smartphone's LED can be irritating to patients when held close to the eye, the D-Eye also has a diaphragm that dims the light, making it more tolerable. Dr. Russo says even babies are not bothered by the illumination.

In practice, Dr. Russo says the field of view is limited. "It's around 5 to 8 degrees with an undilated pupil, and 20 to 25 degrees with dilation," he says. "This is because direct ophthalmoscopy is similar to looking through a keyhole, and the wider the keyhole, the wider the field of view. It really depends on the pupil's dimensions.

"You can record still images or videos with it," Dr. Russo continues, "but I suggest recording video, since you have a limited field of view. In video mode, you can pan around the retina, from the fovea to the optic disk, then out to the equator, to catch all the details. Otherwise, if you only use still images, you could lose a few parts of the retina. You can't go farther than the equator, but you can reach it as you can with an ordinary direct ophthalmoscope."

This article has no commercial sponsorship.

Dr. Russo says that, though the device is useful, it's not a substitute for a traditional retinal camera and direct ophthalmoscopy. "The traditional system is the next level," he says. "The D-Eye system is in the middle between direct ophthalmoscopy and high-end, expensive cameras. This isn't intended to be a substitute for traditional equipment, but instead to help with exams in specific cases, such as bedridden patients, patients in rural areas and babies. In terms of conditions, it's good for glaucoma screening because the optic nerve is easy to view. For diabetic retinopathy, you can assess the retina out to the periphery and notice signs of diabetic retinopathy. We actually published a paper this year that described the agreement between the D-Eye system and the ordinary slit-lamp exam in diabetic retinopathy that found that the agreement was pretty good."[1]

Future plans for the device are aimed at overcoming the current version's limitations. "We're developing a D-Eye 2.0 with a much wider field of view," Dr. Russo explains. "Since, as I said earlier, direct ophthalmoscopy is like looking through a keyhole, the closer you get to the keyhole, the wider the field of view, so the solution is to make the D-Eye slimmer. This one is about 1 cm, and the 2.0 will be 0.5 cm."

The D-Eye costs $390. Also, when a new version comes out, Dr. Russo says all the user will need to purchase is the housing that attaches to the phone, not an entirely new D-Eye lens system. For information, visit d-eyecare.com.

OphthalmicDocs Fundus

The OphthalmicDocs Fundus is born out of the open-source movement in software, which allows users to take a product, in this case an adapter for a smartphone, and modify it in ways they see fit. As such, the OphthalmicDocs adapter isn't something you buy; instead it's a file you can download and send to a 3D printer, creating it yourself for the cost of the printing and materials. You add a condensing lens and then attach the device to your smartphone.

Hong Sheng Chiong, MD

The OphthalmicDocs Fundus is inexpensive because you make it on a 3D printer.

The idea for the device came from Hong Sheng Chiong, MD, an ophthalmology registrar (similar to a resident in the United States) at Gisborne Hospital in New Zealand. At first, his idea was limited to drawings on paper, but when he co-founded OphthalmicDocs he teamed up with product designers and engineers, and the device began taking shape.

The OphthalmicDocs Fundus adapter is basically a bracket that fits on a smartphone. The bracket has an arm that extends outward from the phone and ends in a housing that holds the condensing lens in front of the phone's camera. "For now the adapter is designed to hold a 28-D or a 20-D lens," explains Dr. Chiong. "The 28-D lens is for pediatric cases or infants, and the 20-D lens is mainly for adults. With dilation, the field of view is up to 40 degrees. If the user has a modern smartphone, such as a Samsung Galaxy or an iPhone, its autofocus is used to compensate for a patient's refractive error, up to 5 D of myopia or hyperopia. As for getting good images, we usually recommend using a smartphone that has at least a 5-megapixel camera. We've tried it on older generation phones with 3.2 or 3.8 megapixels, and found that though you would get a picture of the retina, it wouldn't be of good enough quality to tell if the image is drusen or exudate, or if it's a bleed or pigment." The working distance is between 5 and 7 cm away from the patient's eye.

"We've been mainly using it locally in our hospital for patients who present to the emergency department, those too sick to be sent down to the eye clinic, and for neonatal examinations," says Dr. Chiong. "Because we're on the east coast of New Zealand, it's an outreach area, and we have small villages of 500 to 1,000 people who live two hours away from the nearest health-care center. In that type of situation, it's useful for screenings for patients who require a retinal exam. It's also handy in an outreach environment because a conventional fundus camera would be too heavy and bulky to move around, and could be damaged by the rough road conditions."

Dr. Chiong says that, though the adapter is useful in certain situations, it has some limitations, as well. "The strength of the system is that it's portable," he says. "But, like any portable, handheld device, if you try to take a video and there's movement, it will degrade the image quality. The best way to get a good image is to have the patient sit down, and then stabilize the patient's head with one hand while holding the smartphone with the other.

"The pupil size is a huge factor in getting images with the current version of the device," Dr. Chiong continues. "Cases that are challenging for the retinal adapter are patients that don't have a pupil that's easily dilatable. It's challenging in floppy-iris syndrome, for example. Also, like any other fundus camera, it doesn't give you a 3D perception of a lesion, just 2D, so you can't be sure if it's elevated or not."

Future plans center on making the system non-mydriatic. "We're working on a non-mydriatic adapter with a wider field of view," says Dr. Chiong.

"You could actually have up to a 50-degree field of view by incorporating a small, powerful lens after the objective lens and using an infrared light source to get focus to prevent pupillary constrictions."

The 3D printer file can be downloaded at ophthalmicdocs-fundus.org, along with instructions on assembly. If you don't have access to a 3D printer, you can find one near you by visiting 3Dhubs.com.

PEEK Retina

A smartphone solution for retinal imaging that's being used for research outside of the United States is the Portable Eye Examination Kit Retina.

PEEK Retina consists of an adaptor that slides over the top portion of a smartphone, interfacing with the phone's camera, and a software application for focusing the retinal image and organizing the videos and images that the camera captures.

The PEEK system has been used for retinal screening in low-income communities in Kenya, for diabetic retinopathy detection in Botswana and for screening patients for possible malarial retinopathy in Mali. PEEK's designers are also working on incorporating eye tests into the system to allow physicians in the field to perform quick eye exams to get a baseline for a patient's acuity. In the future, PEEK will also have color testing to screen for color-blindness and contrast sensitivity testing.

In terms of availability, it looks like PEEK will arrive in Europe first. "We are currently in the manufacturing stage, and aim to have the PEEK Retina adapter available in early 2016," explains PEEK's Sarah O'Regan. "We should be able to ship it within the European Union—and to non-governmental organizations within the EU who will be responsible for export. We hope to be able to ship to as many countries as possible, and are working with a regulatory consultant on this. We're currently unable to ship PEEK Retina to addresses in the United States until FDA approval has been granted, but we are working on this." For more information or to possibly get involved with PEEK research, visit peekvision.org. REVIEW

Dr. Russo sold the patent for the D-Eye and is an advisor to the company. Dr. Chiong is co-founder of the charitable trust OphthalmicDocs, which doesn't charge for the adapter or app.

1. Russo A, Morescalchi F, Costagliola C, Delcassi L, Semeraro F. Comparison of smartphone ophthalmoscopy with slit-lamp biomicroscopy for grading diabetic retinopathy. Am J Ophthalmol 2015;159:2:360-4.

Looking deeper
Exploring innovation

Shire's Vision for Ophthalmics

At Shire, we're a leading biotech with a global track record for our work in rare diseases and specialty conditions.

Now we're expanding our vision and bringing the same commitment to ophthalmics. Pursuing the promise of new therapies in ophthalmics to address patients' unmet needs.

Just watch.

Visit **Shire-Eyes.com**

Shire

Donna McCune, CCS-P, COE, CPMA

Risk Adjustment Audits For Medicare Part C

Knowing what to expect from a Risk Adjustment Data Validation audit will help to prevent easily avoidable errors.

Q Does Medicare Part C function in the same manner as Medicare Part B?

A No. Although the Centers for Medicare & Medicaid Services regulates Medicare Part C (also known as "Medicare Advantage" plans), they are separate. Medicare Part B is a straight fee-for-service plan, whereas Medicare Part C often operates with a managed-care plan approach. Medicare Part C plans often include coverage for services not covered by traditional Medicare Part B; for example, dental, vision, hearing, preventive care and additional supplemental services.

Q Is beneficiary enrollment in Medicare Advantage plans growing?

A Yes. In 2007, 8.4 million beneficiaries had Medicare Advantage plans. By 2014, this number had grown by 7.3 million people, with 15.7 million beneficiaries enrolled in a Part C plan. The budget is now $156 billion, 30 percent of total Medicare spending.

Q Who pays private insurance companies to manage Part C plans?

A CMS pays the Medicare Advantage plan for each subscriber. The beneficiary's predicted health status and demographics (e.g., age, gender, disability status) determine the amount of payment to the plan. This process is called "Risk Adjustment." It dictates payment to the plans with greater accuracy by predicting the beneficiary's health-care costs.

Q How do the plans collect data on an individual patient?

A Diagnosis codes submitted on claims, along with medical record documentation from inpatient and outpatient facilities and physician offices, provide the necessary risk adjustment data.

Q How does CMS determine the accuracy of the risk-adjusted payments they make to the managed-care plans?

A CMS engages vendors to perform Risk Adjustment Data Validation (RADV) audits to maintain the accuracy of the risk-adjusted payments and the reliability of the data submitted. The medical record must support the diagnosis codes submitted for payment. Advantage plans may be selected annually for RADV audits.

Q Who provides the information to the Advantage plan for submission to CMS when the plan is audited?

A Providers assist the plan by submitting requested medical records to the Advantage plan when the plan is being audited. Often, the records requested are those of patients with numerous diagnoses. By submitting data on these patients, the plan increases the risk score for its patients, which will increase its risk adjustment payment.

Q Should we assume that any records request from an Advantage plan is for a RADV audit?

A No; these plans can and do conduct traditional audits seeking to confirm the medical necessity of a service and/or the proper level of coding, as well as the accuracy of CPT codes submitted for reimbursement. Providers should carefully review the records request. Most risk adjustment audit letters indicate the purpose of

This article has no commercial sponsorship.

the review; if in doubt, contact the vendor performing the audit and ask.

Q Do I need patient consent to release medical records for a RADV audit?

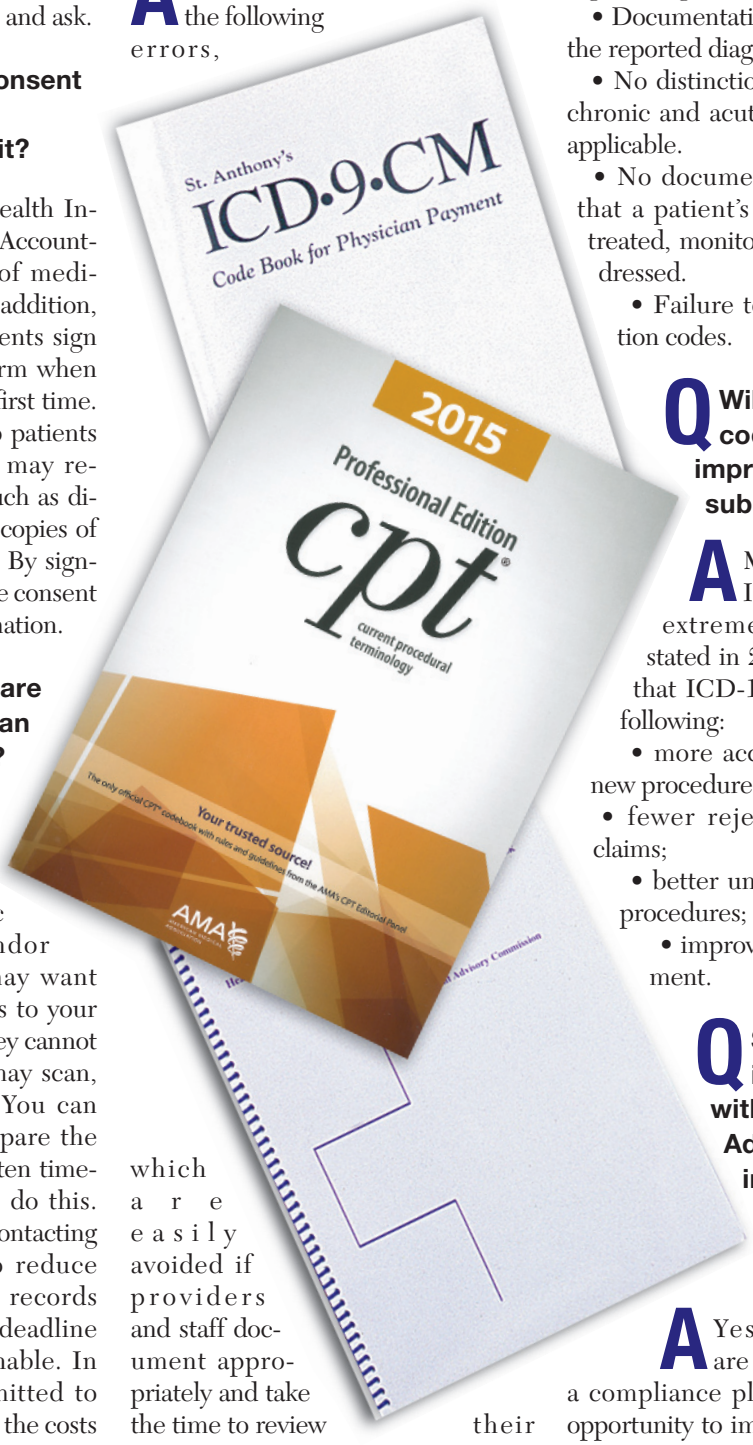
A In general, no. The Health Insurance Portability and Accountability Act allows sharing of medical records with payers. In addition, most practices request patients sign a release of information form when the patient presents for the first time. This form typically states to patients that insurance companies may request clinical information such as diagnoses, treatment plans or copies of their entire medical record. By signing the form, patients provide consent for you to release this information.

Q How many records are requested by the plan to satisfy a RADV audit?

A The plan may request a small number but it may also request a very large number; no magic number exists. The vendor performing the review may want to send one of its reviewers to your office to collect the data. They cannot take original records but may scan, copy or download them. You can refuse this option and prepare the records yourself, but it is often time-consuming for the staff to do this. You also have the option of contacting the vendor and asking to reduce the number of requested records or for an extension if the deadline for submission is unreasonable. In some states, you are permitted to seek payment from them for the costs associated with preparation, staff time and copy costs.

Q What types of errors are found during a risk adjustment audit?

A Audits often reveal the following errors, which are easily avoided if providers and staff document appropriately and take the time to review their documentation and coding:



- The medical record is unsigned or not authenticated with an electronic signature if the practice uses EHR.
- The diagnosis code submitted lacks specificity or is not coded to the highest degree of specificity.
- Documentation does not support the reported diagnoses.
- No distinction is made between chronic and acute conditions, when applicable.
- No documentation to indicate that a patient's condition is being treated, monitored, assessed or addressed.
- Failure to report manifestation codes.

Q Will the ICD-10 coding system improve the data submitted to CMS?

A Maybe. Because ICD-10 codes are extremely specific, CMS stated in 2009 that it believes that ICD-10 will facilitate the following:

- more accurate payment for new procedures;
- fewer rejected or improper claims;
- better understanding of new procedures; and
- improved disease management.

Q Should we include patients with Medicare Advantage plans in our internal and external chart review process?

A Yes. Chart reviews are an integral part of a compliance plan and provide an opportunity to improve the practice's documentation and coding for all payers. REVIEW

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

Postop Inflammation Control in Patients at Risk for IOP Elevation

ERIC D. DONNENFELD, MD, FACS

LOTEMAX® (loteprednol etabonate ophthalmic gel) 0.5% may help control postoperative pain and inflammation in cataract patients who have preexisting glaucoma,* high myopia, or other conditions that could put them at increased risk of steroid-induced intraocular pressure elevation.

Let me begin with a case. I recently performed cataract surgery on the left eye of a highly myopic (–14 D) 59-year-old female. She had previously undergone cataract surgery on her right eye, after which her intraocular pressure (IOP) increased from 17 to 40 mm Hg. Indeed, studies of high myopes demonstrate that they are at greater risk of IOP spikes following cataract surgery than low myopes, especially in patients younger than 65.[1,2]

GOALS OF POSTOPERATIVE MANAGEMENT

Following ocular surgery, many patients have inflammation that can compromise the ocular surface, create pain, and/or induce inflammation in the posterior segment.[3,4] For a number of reasons, postoperative management to control inflammation is an important part of cataract and refractive procedures.[4]

I am focused on a rapid return of visual acuity for my patients. I have also found that my patients want the best possible visual result and recovery without pain. A perfectly performed surgery with great visual outcomes may be viewed as a success by the ophthalmologist but a failure by the patient, if the patient experiences too much pain during recovery.

Dentistry provides a useful analogy: if a dentist fills a cavity perfectly but doesn't provide adequate anesthesia, the patient

*If this product is used for 10 days or longer, intraocular pressure should be monitored.

INDICATION

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

IMPORTANT SAFETY INFORMATION

LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

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

Use of corticosteroids may result in posterior subcapsular cataract formation.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infections.

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

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

Patients should not wear contact lenses when using LOTEMAX® GEL.

The most common ocular adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

will probably not return. Patients who experience pain following cataract surgery may be hesitant to recommend their ophthalmologist.

MANAGING PAIN AND INFLAMMATION

Postoperative pain and inflammation are usually controlled with the use of topical corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs). Both drug classes are clinically useful in suppressing the inflammatory cascade following ocular surgery.[3,4] To manage pain and inflammation after cataract surgery, I use both a corticosteroid and an NSAID because they interrupt the inflammatory cascade at different points and hence are synergistic.[5,6]

Among topical corticosteroids, LOTEMAX® Gel plays a key role in my postoperative antiinflammatory regimen because it is an efficacious corticosteroid with an established safety profile. In an integrated analysis from two prospective, multicenter, randomized, double-masked, vehicle-controlled trials of loteprednol etabonate (LE) gel 0.5% (813 pts; 409 LE gel 0.5%, 404 vehicle), more patients achieved complete resolution of anterior chamber cells with LOTEMAX® Gel vs vehicle at day 8 (31% [126 pts] vs 15% [61 pts]; $P < 0.001$) and day 15 (53% [218 pts] vs 26% [105 pts]; $P < 0.001$). In addition, at day 8, 74.3% (304) of patients in the LE gel 0.5% group reported grade 0 pain versus 43.8% (177) of patients in the vehicle group ($P < 0.001$).[7] Unbound loteprednol etabonate is converted into inactive metabolites, which may result in lower potential for adverse events, such as increased IOP.[8-10] If this product is used for 10 days or longer, IOP should be monitored. I find that the efficacy and safety profile of LOTEMAX® Gel contribute to it being an appropriate option for the management of inflammation and pain following my routine cataract surgeries, particularly in patients at risk of IOP spikes. It is my corticosteroid of choice for patients who have preexisting glaucoma, high myopia, or are known steroid responders.[1]

CHANGING LANDSCAPE

When my 59-year-old female patient returned for cataract surgery on the fellow eye, I prescribed LOTEMAX® Gel four times a day following surgery for 2 weeks.[11] At follow-up visits, her IOP was normal and she recovered uneventfully—with well-controlled inflammation and no pain.

Surgical technology and surgeons' skills have improved over the past decade; cataract and refractive surgery have never been more precise or safe.[12] However, surgery is a controlled trauma, and tissue still reacts to trauma with pain and inflammation. Controlling pain and inflammation remain important.[12,13] My experience is that inflammation and pain that might have been considered par for the course a decade ago are no longer acceptable in modern cataract and refractive surgery.

With our current armamentarium, we have the ability to deliver a surgical result that can provide rapid return of good vision with minimal pain. That's the expectation that I have for every one of my patients, and it's the expectation that most patients have for us when they come to our practice. Patients at risk of elevated IOP can get antiinflammatory efficacy with LOTEMAX® Gel plus an established safety profile that makes this agent my corticosteroid of choice to treat inflammation and pain following cataract surgery.

Eric Donnenfeld, MD, is a partner at Ophthalmic Consultants of Long Island and clinical professor of Ophthalmology at New York University in New York, NY. Eric Donnenfeld, MD, is a consultant to Bausch + Lomb; the content of this article is sponsored by Bausch + Lomb.

REFERENCES

1. Chang DF, Tan JJ, Tripodis Y. Risk factors for steroid response among cataract patients. *J Cataract Refract Surg*. 2011;37(4):675-81.
2. Fan F, Luo Y, Lu Y, et al. Reasons for early ocular hypertension after uneventful cataract surgery. *Eur J Ophthalmol*. 2014;24(5):712-7.
3. El-Harazi SM, Feldman RM. Control of intra-ocular inflammation associated with cataract surgery. *Curr Opin Ophthalmol*. 2001;12(1):4-8.
4. Pleyer U, Ursell PG, Rama P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they the same. *Ophthalmol Ther*. 2013;2:55-72.
5. Wittpenn JR, Silverstein S, Heier J, et al, for Cystoid Macular Edema (ACME) Study Group. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am J Ophthalmol*. 2008;146(4):554-60.
6. Russo A, Costagliola C, Delcassi L. Topical Nonsteroidal Anti-Inflammatory Drugs for Macular Edema. *Mediators Inflamm*. 2013: 476525. doi: 10.1155/2013/476525
7. Rajpal RK, Fong R, Comstock TL. Loteprednol etabonate ophthalmic gel 0.5% following cataract surgery: integrated analysis of two clinical studies. *Adv Ther*. 2013;30:907-23.
8. Bodor N, Buchwald P. Ophthalmic drug design based on the metabolic activity of the eye: soft drugs and chemical delivery systems. *AAPS J*. 2005;7:E820-33.
9. Novack GD, Howes J, Crockett RS, et al. Change in intraocular pressure during long-term use of loteprednol etabonate. *J Glaucoma*. 1998;7:266-9.
10. Howes J, Novack GD. Failure to detect systemic levels, and effects of loteprednol etabonate and its metabolite, PJ-91, following chronic ocular administration. *J Ocul Pharmacol Ther*. 1998;14:153-8.
11. Lotemax® (loteprednol etabonate ophthalmic gel 0.5%) product information. Tampa, FL: Bausch & Lomb; 2012.
12. Ashwin PT, Shah S, Wollfsohn JS. Advances in cataract surgery. *Clin Exp Optom*. 2009;92:333-42.
13. Pager CK. Expectations and Outcomes in Cataract Surgery: A Prospective Test of 2 Models of Satisfaction. *Arch Ophthalmol*. 2004;122:1788-92.

Please see Brief Summary of Prescribing Information on next page.

LOTEMAX® GEL
loteprednol etabonate ophthalmic gel 0.5%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

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

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

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

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

US/LGX/15/0042
Based on 9269100-9269200 Revised: 9/2012

The Dos and Don'ts Of Social Media

Walter Bethke, Managing Editor

How to help patients and your practice while protecting everyone's privacy.

Humans are social animals who love to share their thoughts and feelings. For a long while, this sharing was done in small increments, either over the phone, in-person or maybe with a couple of e-mails. Then, along came social media and the slow drip of the faucet became the blast of the fire hose, allowing everyone to share everything with everybody all the time. Though this sharing can be positive and let people learn new things and feel more connected, it can also blur the lines between the public and the private, as well as the personal and the professional. Though it's a good idea for an ophthalmologist to be up-to-speed and involved with social media, it's easy to fall into some traps while doing so. Here, physicians with a special interest in social media issues share their advice on how to stay out of trouble on social networks.

Separate Your Media Lives

Rather than rushing into the social media maelstrom and being blindsided by a problem, experts say it's good to step back and evaluate why you're doing it.

Jeanne Farnan, MD, an associate professor of medicine at the University of Chicago Medical School, was the lead author on the American College of Physicians' and the Federation of State Medical Boards' position statement on online medical professionalism.[1] "We encourage people to think about what their objectives are when getting involved with or having a presence in social media," she says. "Many have a practice Facebook page and are interested in marketing, while others do it for advocacy. At a national meeting I attend, there will be a tremendous Twitter presence of folks sharing information, so some get involved in social media for educational or scholarly reasons. You should establish some principles ahead of time that will help you when sticky situations arise. For example, I have a LinkedIn profile but not a Facebook one, and I don't have students who are enrolled at my institution as connections, because I'm in an evaluative capacity over them. When they graduate and become residents, however, I'm happy to have them as connections."

Many surgeons, especially younger ones, want to be able to enjoy using social media, but also want to keep their relationship with patients on a professional level. To do this, physicians recommend having two profiles on sites like Facebook. "The main thing is to keep your public social media page professional; don't let anything personal creep in," advises Alex Cohen,

MD, PhD, a corneal specialist in Iowa City who maintains an active social media presence. "This includes such obvious things as not including ridiculous pictures from the weekend but, on a subtler level, remembering that not every patient will agree with your political views or even your views on such things as hunting. If you want to have a personal page for use by friends and family where you can post such things, you might want to create it using an alias. For example, my younger brother has a page that uses a name that's slightly different from his real name."

One issue that arises is when patients want to "friend" you on your personal page. "You need to have a policy up front," says Dr. Farnan. "Here, if a patient sends a friend request, we encourage residents and faculty to ignore the request and then have a conversation the next time the patient's in the office. At that time, say, 'I make it a policy not to share my personal information with patients in order to keep the relationship professional. If you prefer, we can use e-mail or a patient portal.' Patients usually respond pretty well, and don't push the issue." She says having a Facebook page for your practice, as discussed by Dr. Cohen, is a good solution, since patients can friend that and just interact with the practice rather than your personal page. "Many physicians do this," she says, "though there's been a moderate amount of pushback against it from physicians, especially young physicians, who don't want to have to update and monitor two profiles. But, it's important to understand that it's for both your protection and the patient's."

Alex Cohen, MD, PhD

Iowa City corneal specialist Alex Cohen makes sure his social media sites are useful by providing plenty of instructional videos on various types of procedures.

Online Communications

Once you've set up a page where you feel comfortable sharing public information, you also have to concern yourself about what information you and patients share, since health-care information is protected by laws such as the Health Insurance Portability and Accountability Act.

In the atmosphere of sharing on social media, patients will often post health-related questions in the public area of your Facebook page. Physicians say the proper way to deal with these questions depends on the patient and what he's asking. "Communications with patients with whom you have an existing relationship, vs. people you don't know, are different entities, as are general questions about diseases vs. specific questions about a patient's own health," says Dr. Farnan. "The instance of a patient reaching out with a general question about a disease, such as cataract, for example, is a key part of the argument why doctors need to be a part of the conversation on social media. Most adults and teens go online to search for health information. As physicians, we have a responsibility to point them toward resources that are vetted.

"However, if a patient asks via social media about his particular experience with a disease or asks for therapeutic recommendations, that's a different story," Dr. Farnan continues. "Providing answers to questions from patients you haven't seen or examined in the office is a sticky situation. If it's an existing patient of yours whom you've treated and for whom you can easily answer a question in a HIPAA-secure way, then I think the response is up to the physician. A phone call, for example, could handle such a situation and avoid dragging an existing patient into the office unnecessarily. But for someone who's not your patient and who asks a specific question about her health, I think it's better for the physician to say, 'We don't have a relationship yet, so we should do a formal evaluation in the office.' This is because a 'curbside consultation' via a social network page could get a physician into trouble, since the patient might later say, 'The doctor said X or Y to me,' even though the physician never actually saw the patient."

Ravi Goel, MD, a clinical instructor at Wills Eye Hospital who practices at Regional Eye Associates in Cherry Hill, N.J., says electronic medical records make it easier to deal quickly with social media diagnostic questions. "Now that we have moved to EMR, if a patient asks me a question by e-mail or Facebook, I generally call him back and document that I called him in the medical record," he says.

Another, more subtle, danger of the

social media world is the risk patients will view anything you say as your professional opinion as a physician, rather than just one person's opinion on the Internet. "When I speak to medical students, I remind them that there are only two professions in which you actually change your name: the clergy and medicine," says Dr. Farnan. "I'm Dr. Farnan in the hospital and in my practice, but I'm also Dr. Farnan at the store and on the Internet. Representation is a huge issue. So, even though you may not be speaking as a physician when you tweet something like, 'I support this candidate for president,' it may be passively implied. It's important to consider how your comment or message will be perceived by patients, students and colleagues. What will the message say about you, and you as a representative of the profession? Always pause before posting."

Patient-targeted Googling

Today, physicians have unprecedented access to their patient's personal lives and behaviors thanks to social media profiles. Experts continue to debate whether physicians should avail themselves of this information.

The ethical ambiguity of looking up a patient on Facebook, absent any codified guidelines, is illustrated by an example from an editorial in the *Journal of General Internal Medicine*.[2] In it, a patient underwent genetic testing for breast cancer that found certain gene mutations, and resulted in the need to counsel her about mutations that could lead to cancers in the future. However, years later, the genetics lab sent an amended report: A gene variant turned out to confirm a diagnosis of Fanconi anemia, a rare bone marrow disorder. The variant also conferred a 100-percent chance—rather than the initially quoted 50-percent risk—of any offspring also having Fanconi anemia. The patient had been lost to follow-up, however, and the physicians saw Googling her as a requirement in order to notify her of the diagnosis.

Though at first blush ophthalmology might seem immune from behaviors that could be identified on Facebook, there have been cases of unhappy LASIK patients contemplating suicide, patients using unregulated colored contact lenses, at-risk AMD patients constantly smoking and patients fooling around with fireworks. Evidence of all of these behaviors could conceivably be found on a Facebook page. Dr. Farnan says that, in general, it's probably best to avoid the temptation to check up on patients. "It's a two-way street," she says. "We expect patients to respect our private lives, so we should respect theirs. There are many caveats, obviously, such as a patient who's a threat to harm himself or others, but again, you have to ask, 'What's my motivation for checking?' In reality, most who publish in this area agree that it's probably not a good idea. We need to focus on our connection with the patient in the office. In many cases, you can't even determine the validity of what you find; you don't know that the Facebook profile belongs to the person you think it does."

Sharing Case Studies

One of the most useful aspects of social media is the ability to share your patient cases with colleagues (to demonstrate a new technique or request "crowdsourced" advice) or with patients (so they can see what a procedure actually looks like). However, as with other social media posts, you have to be aware of privacy issues.

Dr. Goel says he's seen some questionable things while cruising through pages. "I attend AMA meetings, and I've become friends with young medical students and residents," he says. "And I'll often contact them to let them know there may be some serious HIPAA privacy issues with the cases they recently posted. We're a profession that learns by sharing, so you want to be able to educate colleagues. However, you have to be mindful of patient privacy when discussing any type of clinical or surgical care online."

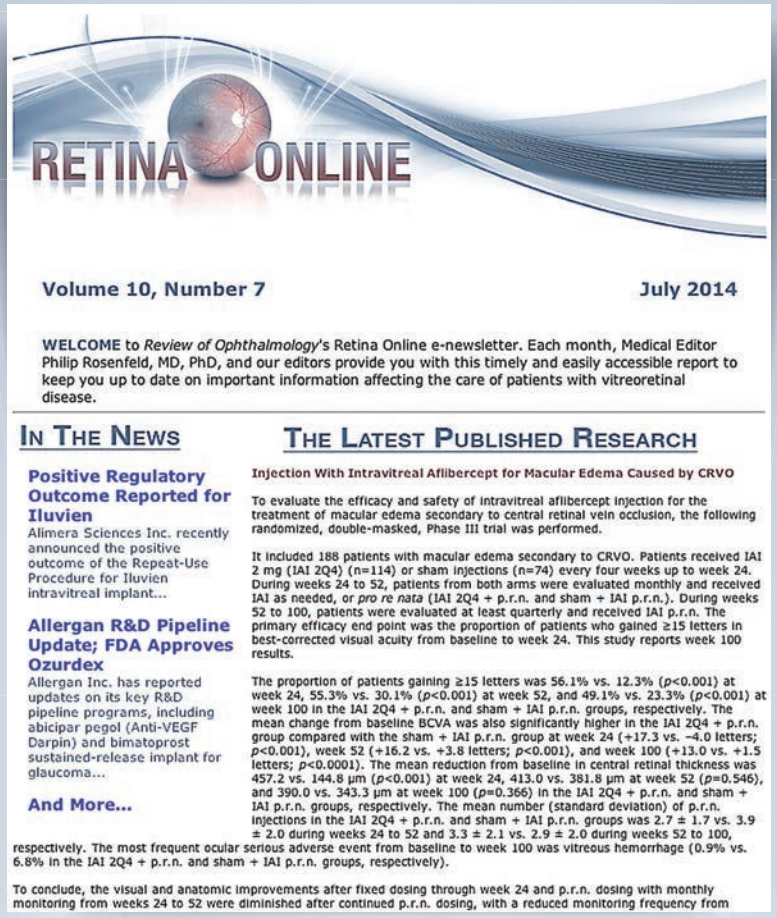
Dr. Cohen says videos are a mainstay of his pages. "My Facebook and YouTube pages are teaching pages," he says. "During my education, I learned a lot from social media, and that's why my pages are dedicated to instruction. I've gotten comments from physicians that one of my YouTube videos helped them learn a procedure."

Posting a surgical case requires that the patient be anonymous, which is relatively easy in ophthalmology since the view is often just of the eye. Sometimes, however, a patient presentation is so specific that extra measures are required. "If the circumstances of the case are unique, I'll often change the patient's gender, his age and sometimes even the circumstances," Dr. Cohen says. "I may even wait a year after the procedure before posting it. However, despite this, if the case remains identifiable, I'll secure the patient's permission."

Ultimately, similar to building an immunity to a virus, Dr. Farnan says frequent exposure to social media will actually teach you how to use it. "It can be tough telling the younger generation to curtail their social media habits," Dr. Farnan says. "But, by the same token, they're more savvy and aware of the pitfalls. And, of course, the people who don't use social media at all can't get into trouble. It's the ones who use it sparingly who often don't understand the full ramifications of what they post. It's the kind of person who lurks on Twitter and then posts something terrible who has to be careful." REVIEW

1. Farnan JM, Sulmasy LS, Worster BK, Chaudhry HJ, et al. Online medical professionalism: Patient and public relationships: Policy statement from the American College of Physicians and the Federation of State Medical Boards. Ann Intern Med 2013;158:8:620-627.
2. Baker MJ, George DR, Kauffman GL. Navigating the Google blind spot: An emerging need for professional guidelines to address patient-targeted googling. J Gen Intern Med 2014;30:1:6-7.

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

Volume 10, Number 7 July 2014

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

IN THE NEWS

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

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

And More...

THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

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

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

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

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

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

3 EASY WAYS TO SUBSCRIBE!

http://www.jobson.com/globalemail/

Fax: 610.492.1039 or Call: 610.492.1027

REVIEW® of Ophthalmology

The Doctor-Patient Connection Goes Digital

Christopher Kent, Senior Editor

Advances in technology are causing significant changes in the way doctors interact with patients.

There's no question that the advent of digital communication, along with the increasing miniaturization and portability of testing devices, is changing the way doctors and patients interact. This brave new world is making it easier for patients to connect with physicians; providing patients with access to large amounts of (non-vetted) information about their conditions; increasing the speed at which tests are conducted and results are visible; and creating a host of new possibilities in terms of diagnosis, monitoring and patient education. These changes are giving the patient more influence over the course of treatment, while at the same time giving doctors new ways to reach patients with information and guidance.

"Patients are partners in their care now more than they were 10 years ago," says Richard M. Awdeh, MD, assistant professor of clinical ophthalmology and assistant professor of ophthalmology and pathology at the Bascom Palmer Eye Institute in Miami. (Dr. Awdeh is the creator of the CheckedUp platform, an educational platform created to facilitate the doctor-patient relationship.) "Ten years ago patients would go to the doctor, the doctor would tell them XYZ, then they'd walk out and that would be it. Today, patients want to be more engaged. They want to be a part of the decision-making process; they want to be informed; they want to understand why decisions are being made. As a result, they're now more actively involved in their care and taking more ownership of their care. I think that's a big change, and I think we'll continue to see more of it."

Here several health-care professionals who are caught up in these changes discuss what they see happening and where all of this may be leading.

Patient Self-assessment

As most physicians are well aware, today's patients are tempted to self-diagnose because of their access to copious amounts of medical information on the Internet. "As a July 2015 Rock Health survey of 4,017 respondents with mobile Internet access showed, the most popular digital health adoption was accessing online health information sites such as WebMD, which 71 percent had done," says Robert T. Chang, MD, assistant professor of ophthalmology at Byers Eye Institute at Stanford University School of Medicine in Palo Alto, Calif. (Dr. Chang is co-developer of the EyeGo adapter, licensed to Digisight Technologies as the Paxos Scope, which facilitates

the capture of high-quality photos of the front and back of the eye using a smartphone.) "Fifty percent indicated historical use of online reviews, but only 17 percent engaged in mobile health tracking, which is often cited as having a steep drop-off after six months. Despite the hype and promise, video-based telemedicine usage was only 7 percent. *(See tables, right.)*

"An increasing number of eye patients in Palo Alto come to Stanford asking about the latest cataract surgery technologies," he continues. "The rapid dissemination of new medical information via the Internet has encouraged the 'democratization of health care.' However, patient online research sometimes leads patients to believe they know more than they do, or induces more anxiety. The problem with reading articles on a site like WebMD is that you may learn something about the condition, but it won't necessarily help you understand the unique aspects of your own condition."

A more ground-breaking tool for self-assessment—at least in theory—is now also becoming popular: vision testing at home using a computer or smartphone. While some medical areas such as blood glucose monitoring might require fairly sophisticated equipment to even attempt home monitoring, the nature of eye problems makes such an approach potentially feasible—at least for certain types of problems.

Ken Lord, MD, a vitreoretinal specialist at Retina Associates of Southern Utah, is the co-developer of The Eye Handbook. (The Eye Handbook is a diagnostic and treatment reference application for eye-care professionals; it's the number-one mobile ophthalmology app, downloaded more than 1.5 million times to date.) Dr. Lord agrees that self-assessment is a trend. "There's a lot of this kind of thing going on," he says. "We don't want to assume any liability as a result of putting something out there that allows patients to test themselves, so we have to be careful. However, patients are going to do whatever they want to do.

"The Eye Handbook app is not designed for patients, so there's no specific patient-use area, but patients are occasionally using it," he continues. "There's a section that allows you to test your vision with a near card and do some color vision tests, although obviously this doesn't replace office-based testing. You can also look up what symptoms of certain conditions might feel like or look like; that's popular with patients. *(See examples on p.32.)* The Eye Handbook doesn't have much competition as a comprehensive eye-care application, but there are at least 100 apps that test color vision and near vision and do other types of vision testing, available on both of the app stores.

"Apps have even been developed to determine a patient's refractive state, along with programs on the computer that allow a person to determine the glasses or contact lenses he needs and order them," he continues. "So far, none of this has been approved by the FDA; you still need a prescription from a doctor to order glasses or contact lenses. But it's becoming a lot more common for patients to try to do a self-assessment. We're living in that kind of do-it-yourself culture. People feel empowered because of current technology, being able to Google medical conditions and treatments. That's definitely the trend.

"I doubt that self-testing will replace the instruments and methodology you

Consumer Adoption of Digital Health Options

Research online health information:	71 percent
Check online health reviews:	50 percent
Use a mobile app to track one or more health-related factors:	17 percent
Own a wearable health-tracking device:	12 percent
Use genetic information services:	7 percent
Use video-based telemedicine to receive care or advice:	7 percent

Consumer Use of Health Information Found Online

Percentage of survey respondents who searched for information online:	
Prescription drug information:	60 percent
Diagnostic information:	57 percent
Information about supplements:	52 percent
Information about treatment options:	49 percent
Percent of the above that acted on information found online:	
Asked doctor to prescribe or discontinue drug:	35 percent
Proposed a diagnosis to the physician:	45 percent
Purchased or discontinued use of a supplement:	40 percent
Proposed a treatment to the physician:	36 percent

Today, multiple companies are participating in the shift toward digital health care. Their offerings can be divided into six overarching categories: online information; reviews of practitioners; mobile fitness-tracking services; wearable tracking devices; consumer-oriented genetic services; and telemedicine. The data above came from a survey of 4,017 consumers done by Rock Health, a venture fund dedicated to digital health. (For more survey results, visit http://rockhealth.com/reports/digital-health-consumer-adoption-2015/.)

find in a real clinic," he adds. "Plus, a lot of people want a complete professional analysis by a physician. But there's a certain segment of our culture that's probably going to use that technology."

Problems with Self-testing

While self-testing is an appealing concept, a number of issues may prevent it from becoming a mainstream medical tool any time soon.

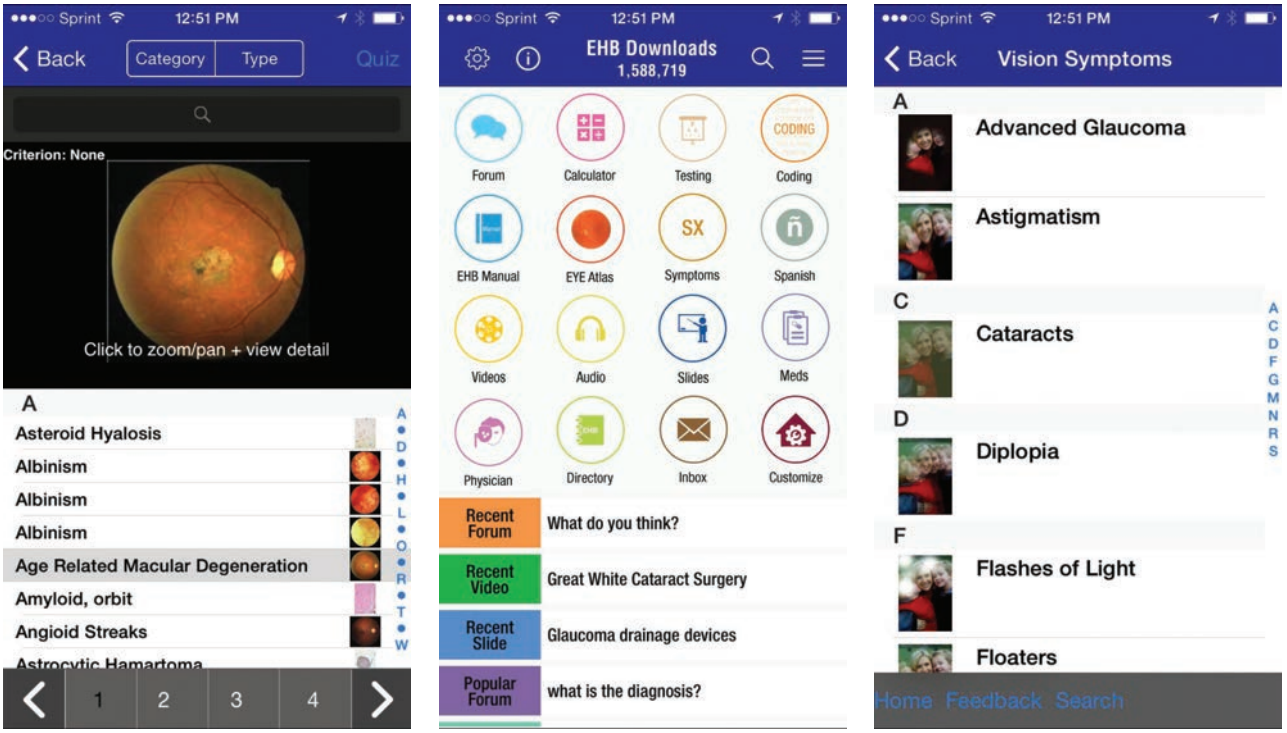
• ***Questionable accuracy.*** Can consumer self-testing be accurate? "Theoretically, yes," says Dr. Lord. "A team at MIT is developing an app and smartphone device that should be able to determine what the refractive state of the eye is; they hope to market it within four years. The user will look through a series of lenses and projections in the device. There are similar programs in development that don't even need a device attached to the smartphone. Their accuracy remains to be seen."

• ***Lack of validation.*** Simply being an accurate test isn't enough. "Many apps allow you to test your vision on your smartphone at home—a low-hanging-fruit medical test," notes Dr. Chang. "The problem is that there is no oversight to ensure quality control of data collection, and home testing is just starting to be validated against gold standards. If physicians are going to make a medical decision based on a consumer digital device measurement, they want to see FDA medical-grade validation."

• ***It's only one measurement.*** Dr. Chang points out that self-testing doesn't constitute a full exam. For many medical decisions the doctor needs multiple pieces of information that may be impossible to collect at home. "For example, it's difficult to think of a situation where visual acuity alone would be to make a medical decision," he says. "It's like a vital sign; we still need other diagnostic information to conclude what's going on with the vision change. However, if we were to start combining multiple pieces of information such as visual acuity and refraction measured by a tool like the Smart Vision Labs SVOne, with eye pressure measured by a tool like I-Care Home, and smartphone photos of the front and back of the eye, plus a portable OCT of the retina, then remote telehealth might be more readily accepted by practitioners. Until then, remote testing is more like remote triage—it primarily helps determine the level of urgency or severity of the problem."

Smartphone technology is helping to make eye examinations more portable. Above: the Paxos Scope (DigiSight Technologies), a universal smartphone adapter that allows doctors to capture high-resolution anterior and posterior images of the eye.

• ***It may not be actionable information.*** Another problem with current consumer health monitoring technology is that it often provides data that is not actionable yet—even if it were validated. "A device like the Fitbit can monitor your heart rate all day, but what is the actionable information?" asks Dr. Chang. "Most people who care enough to monitor their exercise probably don't need the device to help them to exercise more; it simply appeals to their quantitative side. Right now, we have a data collection problem since we don't know what to do with all the big data coming from daily monitoring. The hope is that some new insights will arise from all the shared data in the future, but machine-learning research will be



Above: Sample screens from The Eye Handbook app (created by Cloud Nine Development), a popular free diagnostic and treatment reference for eye-care professionals. Although the app was not intended for patients, sections that explain what different conditions look or feel like (above, right), as well as some basic near and color vision tests, have become popular with many patients.

needed to sort it all out."

Dr. Chang acknowledges that some of today's digital monitoring is, in fact, actionable. "Real-time blood glucose level monitoring in some individuals is actionable because you may need to give medicine directly related to an individual value; too high or too low a value might have dire consequences," he says. "Thus, those situations are where digital health will first make a difference. Another example of digital therapeutics having a sustained impact is Omada Health, the first digital-health start-up to have published positive two-year results demonstrating that their Internet program helped participants maintain clinically meaningful reductions in weight and hemoglobin A1c. Whether something like that will apply to eye care, such as chronic glaucoma therapy compliance, remains to be seen."

Dr. Chang does point out that non-actionable data from large numbers of people in a population might be useful in other ways. "It helps with population-based data analysis," he says. "For example, thanks to these digital health apps, researchers have gathered unprecedented amounts of activity data from tens of thousands of individuals in a very short amount of time from the MyHeartCounts app. That kind of information may allow us to make better public-health decisions."

Despite the limitations of self-testing, Dr. Chang does sees potential in it. "At some point in the future, it may be possible to prescribe home monitoring that will catch the earliest signs of a problem, before the patient can tell something is abnormal," says Dr. Chang. "That device will be more useful as a remote measurement tool. Today there is one FDA-approved home-monitoring vision test: The ForeseeHome AMD Monitoring Program from Notal Vision. It helps patients detect central and paracentral metamorphopsia as an aid in monitoring progression of the disease. But it still must be prescribed by a physician. In the meantime, a lot of information from consumer devices falls into the category of new data that we don't know what to do with yet, since it's never been collected in this manner. However, companies and researchers are eager to find the added value and sensitivity/specificity levels of new diagnostics.

"At the same time," he adds, "having an app quantify exactly how much vision loss you're experiencing may be unnecessary if your vision is already bad enough to make you want to see a doctor directly."

Digital Communication

With a handy communication device in most people's pocket, doctors and patients are able to reach each other (or at least leave a message) at

almost any time or place.

"Being able to communicate with your doctor is highly valued because people feel more satisfied when they have better access to their doctors the moment they need it," says Dr. Chang. "That's why non-urgent telemedicine via email has caught on. It's a way of streamlining the older process where patients would call the office nurse, who wrote a note and handed it to the doctor, who gave an answer back to the nurse, who called the patient back. Now simple questions and refill requests can be completed entirely electronically."

Digital communication, of course, is a two-way street; in addition to making it easier for patients to contact their doctors, it also makes it easier for doctors to reach patients with important information relevant to their condition and treatment. However, Mark M. Prussian, MBA, FACHE, chief executive officer at The Eye Care Institute in Louisville, Ky., notes that having a digital channel to communicate doesn't always result in communication. "The Eye Care Institute sends out patient information sheets through the practice's EHR system, to educate patients and to comply with Meaningful Use requirements," he says. "Unfortunately, our anecdotal evidence indicates that the patients often don't read what we send.

"We continue to have amazingly strong success with our e-newsletter, which is now more than 10 years old, but this is a one-way push of information from us," he continues. "We know it's successful because with each newsletter we get between 50 and 100 responses asking for everything from more information on the topics we covered in the newsletter to how much is the patient's balance due. In addition, we've used a patient portal for more than six years; we encourage our patients to ask us clinically relevant questions using the portal. We've found that very few patients use the portal, and those who do often ask about their balance due or their next appointment time. There aren't many interactions where the patient's medical care or vision outcome is enriched by having the portal."

Of course, one Internet resource is now used by nearly every doctor: a practice website. "All the doctors we work with ask us what's important to have on their website," says Dr. Awdeh. "I'd say there are two ways practices go when setting up their websites. Most use their website for three things: search engine optimization, to ensure that when a patient searches for a doctor in that area their practice comes up; providing patients with a way to make an appointment; and providing directions to the office. Some practices make their websites more complex, adding a blog and basic patient education, such as descriptions of diseases, but making a complex website can be challenging. It's hard for one practice to build the type of website you'd be able to create if you were doing it in concert with hundreds of other practices. And it's not clear how much a more complex website pays off."

Digital Patient Education

A number of innovators are working to take better advantage of the potential of digital communication. Dr. Awdeh says his creation, the CheckedUp digital platform, helps practices keep pace with today's technology. "CheckedUp is designed to take advantage of all the types of technology we're accustomed to using in our everyday lives," he says. "I created it because of the contrast I saw between our day-to-day use of technology outside the office and what was happening in the clinic, where I was explaining things to patients and then either having them watch a DVD or handing out a photocopy brochure.

"I noted that these traditional edu-

The CheckedUp platform allows patients to access information relevant to their specific medical situation, chosen by the physican, at any time or location through a secure HIPAA-compliant portal. The platform also includes information stations placed in the practice (example above).

cational methods are not very effective," he continues. "The volume of patients doctors are responsible for has gone up. As a result, the amount of time per patient that a doctor spends conducting an exam has gone down over the past 10 years. That's made it harder for the treating physician to find out what's going on with the patient, to have a value-driven conversation where you're able to focus on things that are important to the patient.

"This problem is compounded by all the new options we have to discuss with patients," he notes. "When we're talking to a new cataract patient we have to discuss different surgical techniques and implant options. Ten years ago we just had monofocal lenses; now we have torics, multifocals and accommodating lenses. Looking at presbyopia, we used to have nothing to offer. In the next few years we're going to have several options for addressing presbyopia, from corneal inlays to presbyopia-correcting IOLs, to pharmacologic solutions. So the conversation we have to have with the patient has become fairly complex, and we need to have it in a shorter amount of time, under the umbrella of the patient wanting to understand it and be a partner in his care.

"My patients were asking the same questions over and over again and having trouble retaining things they were told in the clinic," he continues. "I decided that there had to be a better way to manage this, one that would allow patients to re-access that information and let them revisit things we discussed in the clinic whenever and wherever they wanted. The reality is that patients who are better educated are more engaged in their care and have better adherence to the things that we ask them to do before and after a procedure. They are much more comfortable with their diagnosis and they play a more active role in the care program that we put together for them.

"Ideally, patient education can happen before, during and after the office visit," he says. "It can also happen before or after going to the surgical center, or following a treatment when it's necessary for the patient to continue to be adherent. We've designed CheckedUp to facilitate patient education in all of those situations. It gives patients the details that a healthcare provider would provide for their specific procedure or diagnosis. The patient portal allows patients to ask questions and find answers, engaging the patient in a way that reading a brochure or watching a DVD does not. CheckedUp also includes a follow-up component; it provides data metrics to the practice showing how it's doing at engaging and educating patients and how adherent their patients are. There's also a follow-up program geared to each individual patient based on the patient's education and adherence to the plan."

Dr. Awdeh notes that the information patients access through CheckedUp is significantly different from what they may learn from surfing medical sites on the Web. "The CheckedUp platform is customized to each doctor and tailored to every patient's specific care plan," he says. "The patient may find information online that's broad or universal, but the goal here is to provide information customized by the patient's doctor and tailored to that patient, based on the patient's specific diagnosis or condition. The feedback data provided to participating practices also allows our team to keep improving the educational material accessed by patients. We can see whether patients are responsive to certain types of education or not, and we're able to change the information and presentation based on how patients interact with it. The CheckedUp platform also includes stations that are placed in the clinics." *(See example, above, left.)*

Dr. Awdeh says that specific content and instructions from the treating physician are loaded into the platform through a practice portal and made available to patients through a patient portal, as well as at the clinic stations. "The portal gives each patient unique access, based on their current treatment," he notes. "We've invested in a technology stack that includes best-in-class HIPAA security and data encryption. And of course, we want to make sure that doctors and patients have a very good experience when using it."

Digital Strategies

To make the most of this shifting landscape, Dr. Lord suggests taking a few basic steps:

• ***Check for helpful apps.*** "In addition to publishing the Eye Handbook app, we've created a number of apps designed to help patients manage their connection to your practice," he says. "For example, there's an app that the patient can keep on her phone that lets her contact you, and there are apps that help patients track their medications or review their patient profile. These apps are intended to serve as a complement or companion to your website."

• ***Make sure your website is mobile-friendly.*** "Having a website is key, but it has to be mobile-friendly," says Dr. Lord. "Survey data is showing a clear trend: Patients are spending less time on their home computer and more time on their mobile devices—even when they're at home. It's easier to be on your phone than on your computer. Most of my patients are over 70, but they are pretty tech-savvy."

• ***Make sure your practice is registered on the major search engines and doctor-review sites.*** "There are currently five or six well-known Internet sites at which patients write reviews of doctors and practices, such as Healthgrades," he notes. "You want your practice to be seen on these sites. And you have to have your business up on the major search engines—certainly Google and Yahoo. They have business app portals; if you want to show up near the top of the list on their search engines, you have to be registered with them. Being visible on these sites and search engines is key for any successful practice in today's market. That's where people are searching for eye care.

"As a retina specialist, I don't advertise to the general public at all, but I am on the Internet," he adds. "If you search for retina specialists in my region, you will find me."

• ***Keep in mind that having a practice website may not be sufficient.*** "It's clear that you can't just put up your shingle on Main Street and expect to do well today; but having a website, by itself, isn't sufficient either," says Dr. Lord. "Some practices will definitely benefit from a presence on social media, such as Facebook, Twitter and Instagram. Yes, you need to have a good, mobile-friendly webpage, but you should have a lot more. Your web page should only be 25 percent of your Internet presence." *(For more on this, see "The Dos and Don'ts of Social Media" on p. 25.)*

• ***If you're not tech-savvy, get help.*** "Many doctors, like me, are very tech-savvy," says Dr. Lord. "I read up on this subject to stay current. But if you're not inclined to focus on this, consider getting help. There may be someone on your staff who would be really good at managing this type of thing; I have people in my office who help me keep up. If you feel you could

(continued on page 63)

The Landscape Keeps Shifting

In addition to changing the ways in which information is captured and shared, evolving technology is also leading to a number of new options that are making patient care easier to access:

• ***Seeing a doctor on the Web.*** Having a virtual consultation with a doctor over the Internet is a growing trend. "Companies such as Healthtap are offering to connect patients with a doctor via the Internet," says Ken Lord, MD, a vitreoretinal specialist at Retina Associates of Southern Utah. "The patient doesn't even have to go to an office. The patient can just register with the website and pay a fee—some of them do it for free initially—and ask the doctor a question, via text or video chat. Doctors can participate by registering at the website. Doctors make less money than they would seeing patients in the office, but for the right practitioner it might be an attractive option. You can work from home or the beach or the airport, answer a few medical questions and get paid. The idea of a virtual consultation is becoming more popular and probably will continue to do so."

Such a consultation would clearly not allow a detailed eye exam, but might allow an ophthalmologist to act as an advisor when a patient has a concern.

• ***Taking the refractive exam to the patient.*** Another way in which the digital revolution is impacting medical care is by making some processes portable that previously were not. "For example, New York City start-up Blink is providing an on-demand refractive eye exam service," says Robert T. Chang, MD, assistant professor of ophthalmology at Byers Eye Institute at Stanford University School of Medicine in Palo Alto, Calif. "A customer orders an eye exam online and a technician arrives at the consumer's home or office with portable, smartphone-based refractive equipment called Eyenetra, developed at the Massachusetts Institute of Technology Media Lab. The Eyenetra devices collect the information needed to prescribe glasses; that information is confirmed by an optometrist who emails the consumer a prescription for glasses within 24 hours. *(You can find out more at goblink.co.)* This is part of the online-to-offline business model for metropolitan areas."

• ***Live remote translation services.*** "Working in an academic university medical center, we are lucky to have access to live webcam translators," says Dr. Chang. "The outsourced translation services were never that good, and now our full-time employed translators can use technology so they don't have to travel around the hospital as much. While Google Translate has also markedly improved, the machine learning algorithm still has trouble with sentences and complicated medical explanations; thus, I still find it most useful for simple commands."

—CK

CME

FEBRUARY 13-14, 2016

Ophthalmology Update 2016

PROGRAM CHAIRS

Don O. Kikkawa, MD
Robert N. Weinreb, MD

DISTINGUISHED INVITED SPEAKERS

Kerry Assil, MD
Helen Danesh-Meyer, MD
Robert A. Goldberg, MD
Jeffrey M. Liebmann, MD
Ken K. Nischal, MD
Srinivas R. Sadda, MD
Ningli Wang, MD

LOCATION

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

3 WAYS TO REGISTER

Call Lois DiDomenico: 877-451-6513
Online: www.ReviewofOphthalmology.com/Update2016
Email: ReviewMeetings@Jobson.com

Please check www.ReviewofOphthalmology.com/Update2016 for up-to-date information.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Health Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians

Credit Designation Statement
IAHB designates this live activity for a maximum of 11.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

UC San Diego Shiley Eye Center

Jointly provided by
IAHB PHE

Review of Ophthalmology®

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

Discounted room rates available at $219/night. Limited number of rooms available. See registration site for more information.

Photos: ©2015 Hilton Hotels & Resorts

EDUCATIONAL OBJECTIVES

- Analyze new research that illustrates the key role that inflammation plays in the genesis of DME and macular edema secondary to RVO.
- Engage in discussions related to emerging issues in glaucoma, including risk assessment, imaging, management and progression assessment.
- Manage glaucoma using newer pharmaceutical agents.
- Discuss the newest glaucoma surgical devices, including those used in patients undergoing cataract surgery.
- Utilize advanced technologies and techniques in refractive cataract surgery, including femtosecond laser and new ultrasound fluidics.
- Master advanced technology IOLs, improving patient selection, surgical technique and postoperative management.
- Outline current management techniques for ocular surface diseases such as dry eye and keratitis.
- Discuss the rationale for anti-VEGF therapy and steroids in posterior segment diseases including age-related macular degeneration and diabetic macular edema.
- Navigate issues relating to patient compliance/adherence with eye-drop medications.
- To understand the facial aging process and gain knowledge of possible treatments for rejuvenation.

PROGRAM TIMES

Saturday, February 13
8:00am — 5:00pm
Reception to follow
Sunday, February 14
8:00am — 12:15pm

UC San Diego Shiley Eye Center

Jointly provided by
IAHB PHE

Review of Ophthalmology®


Shifting Focus in Retinal Implant Development

Moving beyond the proof-of-concept stage, a greater emphasis on the functional outcomes of retinal implants is needed.

Alice T. Chuang, MD, San Jose, Calif., Curtis E. Margo, MD, MPH, Tampa, Fla., Paul B. Greenberg, MD, Providence, R.I.

In the last decade, retinal implants, or prostheses, have gone from futuristic research projects to reality. Devices have gained Food and Drug Administration approval in the United States and CE marking in Europe for the purpose of vision restoration in persons with advanced degenerative retinopathy. Several research groups have led the forefront of this field, as each approach to this elaborate engineering process encounters unique challenges.

The collective experience with retinal implant development has also shifted focus at different junctures to meet these challenges. From numerical, hardware-based, proof-of-principle experiments, emphasis is now moving towards optimizing the tissue-device interface of existing implants to improve patients' quality of life. In particular, two devices with the most clinical availability, the Argus II (Second Sight Medical Products, Sylmar, Calif.) and Alpha IMS (Retina Implant AG, Reutlingen, Germany), demonstrate a modified trajectory in prosthetic research and serve as models for optimization of retinal implants.

Background

Two retinopathies that have the greatest potential benefit from retinal implants are retinitis pigmentosa and age-related macular degeneration. Retinitis pigmentosa is a hereditary degenerative disease of the outer retina-retinal pigment epithelium complex, with relative sparing of the inner retina and upstream visual pathway. Visual impairment generally presents in early to mid-adulthood and can progress to hand-motion or light-perception visual acuity. Currently, there is no available disease-modifying treatment. Similarly, age-related macular degeneration, the most common cause of severe visual impairment in older adults, presently has no available cure. Typically, central vision is lost with sparing of peripheral vision, while visual processing is retained upstream.

Retinal implants have been primarily tested in patients with hand-motion or light-perception vision. They are placed in the worse eye, augmenting retinal tissue presumed minimally functional. Best attained visual acuity to date has been Snellen 20/546 by the Alpha IMS, though outcome emphasis is now shifting towards assessing functional improvement in daily life, using scores such as the Functional Low Vision Observer Rate Assessment (FLORA). Many research groups have developed distinct models of retinal implants, most of which are being studied *in vitro* or in animals. Only Argus II has received both FDA approval (2013) and CE marking (2011).[1] Alpha IMS received CE marking in 2013.[2]

One means of classifying retinal implants is by insertion position—either epiretinal or subretinal. Epiretinal devices, such as the Argus II, are surgically more straightforward to place, but require stabilization by retinal tacks that increase rates of scarring and gliosis, or complicate implant removal. Functionally, these implants bypass the outer retina, interfacing directly with upstream neuronal cells. Subretinal devices, such as the Alpha IMS, are surgically more difficult to insert, but do not require tacks, as the natural forces within the eye tamponade the implant in position. Functionally, these devices aim to replace degenerated photoreceptor cells.

A second means of classifying retinal implants is by image-acquisition

technology. External cameras are used in the Argus II, while intraocular photosensitive elements are used in the Alpha IMS. In both modalities, pixel number was initially thought to be a primary determinant of image quality. However, recent literature suggests that crosstalk between individual electrodes, distance from each electrode to interfacing tissue and frequency, rather than intensity of conduction, may play more important roles than previously believed. Further research should clarify the interaction among each of these factors. Currently, a multifactorial effect is assumed.

Argus II

The Argus II is the second-generation device by Second Sight, which has a collaborative affiliation with the University of Southern California. The system consists of an epiretinal implant, an episcleral image processor, an external camera and a battery pack. The Argus II was the first retinal implant to receive CE marking, and the only implant granted an FDA approval as a Humanitarian Use Device. Currently, it has been implanted in more than 70 patients. Research is ongoing, and has documented improvement in visual acuity (best achieved 20/1,262) and task completion with the 60-electrode array. Increased emphasis has been placed on functional improvements, using measurements such as the FLORA score.[3,4]

Common complications with the Argus II include conjunctival erosion and retinal tack gliosis (form of retinal scarring). Other complications include endophthalmitis, hypotony and retinal tears/detachment. Most of the complications occurred in patients involved in earlier studies; complication rates decreased with improved procedural protocols, clinical experience and device modification. The longest retention time for an implanted Argus II is 7.2 years, and for Argus I it is 10 years. Long-term biocompatibility is favorably reflected by these examples of visual improvement with stable safety profiles.[5]

Alpha IMS

The Alpha IMS has been developed by the Retina Implant AG group at the University of Tubingen, Germany, and has received CE marking. The device consists of a subretinal 1,500-photodiode array that interfaces with the bipolar cell layer of the inner retina, and a subdermal electronics case behind the ear. The current clinical trial consists of 29 patients, with increased success in visual tasks (best-achieved Snellen, 20/546) as the trial progressed.[6] Although optimization of implant engineering and insertion was continued throughout the trial, researchers have theorized that a nontrivial portion of the functional restoration by subretinal implants may be from localized physical and electrical stimulation.[7] Alterations in subretinal tissues through electrical stimulation (e.g., increased release of growth factors) may be a potential direction for further investigation.

The safety profile in the current Alpha IMS study showed the most common complications were conjunctival erosions and elevated intraocular pressure. Rarer complications were retinal tears/detachment, and one case of accidentally intraoperatively touching the optic nerve and perforation of the choroid. Similar to the Argus II, these complications decreased as the study progressed. Overall, more complications were associated with the initial implantation procedure, which is understandable given the higher complexity of subretinal compared to epiretinal insertion. The longest retention time for the Alpha IMS was 1.9 years.[8]

Better Outcomes, New Directions

With the recent clinical availability of retinal implants, translational research may be the ideal means by which to continue device development. Through the dynamic balance of updating research goals to match clinical needs, further optimization can continue to improve the utility of retinal implants. In many ways, this process has already begun: The objectives of research have moved from proof-of-principle and safety to achieving surgical finesse in maximizing implant benefit. Patient criteria have changed, as those with visual acuity below 20/800 may now be offered retinal implants in clinical trials in an effort to preserve more vision before it is lost. [7] Methods of optimization of implants have additionally shifted from hardware to software, by focusing on reducing crosstalk between electrodes, increasing edge detection instead of brightness/contrast alone, and balancing conduction frequency to limit flickering without allowing image fading.[2,7,9]

Measurements of outcomes have moved from visual acuity, phosphene detection and detailed experimental tasks, to functional assays, such as the FLORA score in assessing the impact of retinal implants on patients' daily life. Studies have also investigated Quality Adjusted Life Years with retinal implants, annual cost to care for patients disabled by retinitis pigmentosa (~$15,000), and estimated retinal implant cost (~$100,000 to $115,000). Given that the average age of disability in retinitis pigmentosa is in early to mid-adulthood, the cost-to-benefit ratio favors the devices. This trend should continue as outcomes improve and technical cost of production declines.[10,11]

To continue retinal implant development, researchers may find increased collaboration between research groups beneficial. Previously, this type of interaction was limited by the small number of clinical and pre-clinical devices. The proprietary nature of early product

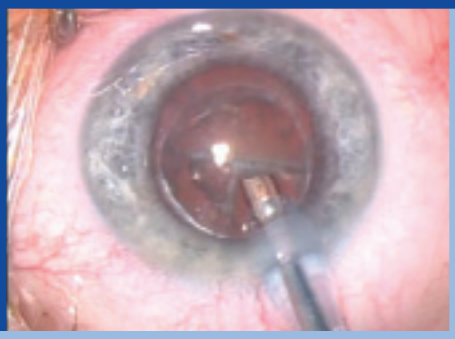
development was another important concern. However, the opportunities to learn from shared experiences may now outweigh these obstacles. Research will tend to shift from physical parameters of designing and building devices to adjusting the electronic-tissue interface and maximizing the efficiency of systems already found to be biocompatible through prolonged clinical trials. This may include altering surgical techniques, which should be facilitated with each additional case performed, as demonstrated in decreasing complications over time in previous studies.

In summary, multiple devices have demonstrated significant benefit in controlled experimental settings, but these measures may be insufficient clinical surrogates as more advanced devices are developed. As research moves forward, greater emphasis on functional outcomes will be needed to fully appreciate the role and benefits of retinal implants. REVIEW

Dr. Chuang is an internal medicine resident at the Santa Clara Valley Medical Center. Dr. Margo is a professor of ophthalmology, and pathology and cell biology at the Morsani College of Medicine, University of South Florida. Dr. Greenberg is a professor of surgery (ophthalmology) at the Warren Alpert Medical School of Brown University. Dr. Greenberg may be reached at: paul_greenberg@brown.edu.

Drs. Chuang, Margo and Greenberg all share a special interest in retinal prosthetic research and the processes by which new technologies become integrated into clinical practice. They declare no financial interest in any product discussed.

1. Yue L, Falabella P, Christopher P, Wuyyuru V, et al. Ten-year follow-up of a blind patient chronically implanted with epiretinal prosthesis Argus I. Ophthalmology 2015 Sep 16. pii: S0161-6420(15)00785-X.
2. Zrenner E. Fighting blindness with microelectronics. Sci Transl Med 2013 Nov 6;5(210):210ps16.
3. Luo YH, Zhong JJ, da Cruz L. The use of Argus II retinal prosthesis by blind subjects to achieve localisation and prehension of objects in 3-dimensional space. Graefe's Arch Clin Exp Ophthalmol 2015 Nov;253(11):1907-14.
4. Stronks HC, Dagnelie G. The functional performance of the Argus II retinal prosthesis. Expert Rev Med Devices 2014 Jan;11(1):23-30.
5. Ho AC, Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Handa J, Barale PO, Sahel JA, Stanga PE, Hafezi F, Safran AB, Salzmann J, Santos A, Birch D, Spencer R, Cideciyan AV, de Juan E, Duncan JL, Eliott D, Fawzi A, Olmos de Koo LC, Brown GC, Haller JA, Regillo CD, Del Priore LV, Arditi A, Geruschat DR, Greenberg RJ; Argus II Study Group. Long-term results from an epiretinal prosthesis to restore sight to the blind. Ophthalmology 2015;122:1547-54.
6. Stingl K, Bartz-Schmidt KU, Besch D, Chee CK, et al. Subretinal visual implant Alpha IMS--Clinical trial interim report. Vision Res 2015 Jun;111(Pt B):149-60.
7. Chow AY. Retinal prostheses development in retinitis pigmentosa patients-progress and comparison. Asia Pac J Ophthalmol 2013 Jul-Aug;2(4):253-68.
8. Kitiratschky VB, Stingl K, Wilhelm B, Peters T, Besch D, Sachs H, Gekeler F, Bartz-Schmidt KU, Zrenner E. Safety evaluation of "retina implant alpha IMS"--a prospective clinical trial. Graefe's Arch Clin Exp Ophthalmol 2015 Mar;253(3):381-7.
9. Kiral-Kornek FI, O'Sullivan-Greene E, Savage CO, McCarthy C, Grayden DB, Burkitt AN. Improved visual performance in letter perception through edge orientation encoding in a retinal prosthesis simulation. J Neural Eng 2014 Dec;11(6):066002.
10. Vaidya A, Borgonovi E, Taylor RS, Sahel JA, Rizzo S, Stanga PE, Kukreja A, Walter P. The cost-effectiveness of the Argus II retinal prosthesis in retinitis pigmentosa patients. BMC Ophthalmol 2014 Apr 14;14:49.
11. Miller A. Retinal implant system delivers limited sight to some blind people. CMAJ 2013 Oct 1;185(14):E659-60.



Save the Date

INNOVATIVE TECHNIQUES & Controversies in Ophthalmology

15 CME Credits

February 12-14, 2016 • Park City, Utah
Grand Summit At Canyons

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

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

Co-Director
Robert J. Cionni, M.D.
Salt Lake City, Utah

Co-Director
Stephen S. Lane M.D.
Minneapolis, Minnesota

- Steven Charles, MD, FACS, FICS
- Garry P. Condon, MD
- David A. Crandall, MD
- James A. Davison, MD, FACS
- Kendall E. Donaldson, MD
- Nicole R. Fram, MD, FACS
- Susan M. MacDonald, MD
- Irving M. Raber, MD
- Sheri L. Rowen, MD
- Mitchell P. Weikert, MD
- Elizabeth Yeu, MD

Schedule of Events
Agenda session times have changed this year

Friday, February 12	Saturday, February 13	Sunday, February 14
3:00 - 4:00PM Registration	5:45 - 6:30AM Registration/Breakfast	5:45 - 6:30AM Registration/Breakfast
4:00 - 7:00PM Evening Sessions & Working Dinner	6:30 - 12:00PM Morning Session	6:30 - 12:00PM Morning Session
	4:00 - 7:00PM Evening Session	

*Agenda is subject to change

Hotel Information:
Grand Summit at Canyons
4000 Canyons Resort Drive
Park City, Utah 84098

Discounted room rates are limited and based on availability, so please book early! Call the hotel directly at 888-226-9667 and identify yourself as a participant of the **Park City Symposium.**

REGISTER NOW!
www.RevOphth.com/ParkCity2016

For more information, check the registration site for faculty, agenda & number of credits or email dholmes@postgradhealthed.com or call 866-627-0714

Physicians
This activity has been designed to meet the educational needs of ophthalmologists, ophthalmology residents and fellows, and other physicians and healthcare professionals involved in the care of cataract and refractive surgery patients.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). The IAHB is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement
The IAHB designates this live activity for a maximum of 15* *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.*

Endorsed by
Review Of Ophthalmology

Jointly Provided by:
IAHB Institute for the Advancement of Human Behavior & PHE

Partially supported by an unrestricted independent medical educational grant from
Alcon


Treat the Patient—Not Just the Disease

Managing a patient's ailment may not alleviate the patient's suffering. Changing our focus can make a world of difference.

George L. Spaeth, MD, Philadelphia

Back in the 1980s, Dewitt Stetten, MD, PhD, a professor of chemistry at Harvard Medical School, wrote an article that appeared in *The New England Journal of Medicine* describing his experience being seen by an ophthalmologist after developing age-related macular degeneration.[1] Back then, of course, we had no effective way to treat this disease. At the end of the exam, the ophthalmologist told Dr. Stetten there was nothing that could be done and sent him on his way. Dr. Stetten was outraged that the doctor made no attempt to help him, simply because he couldn't cure the disease.

As ophthalmologists, we tend to think of preserving vision as our primary responsibility. But the reality is that many of our patients will lose vision despite our best efforts, and that loss brings with it a host of challenges that can undermine a patient's quality of life and functionality. I would argue that, as physicians, our true responsibility is not just to preserve vision but to help our patients maintain functionality and quality of life. Maintaining the patient's vision is simply a means to that end.

Helping patients maintain their functionality and quality of life is well within our abilities as doctors. However, in order to do that we have to be thinking about more than simply managing the patient's vision. We have to remember that our goal is to treat the patient, not just the disease.

Physician, Heal Thy Patient

As doctors, we've become more powerful at manipulating the manifestations of disease, but I don't think we've become any better at understanding how to care for the people who have the disease. For example, I frequently see articles on how to manage glaucoma, but I seldom see articles on how to care for patients who have glaucoma. The difference is huge, and rarely recognized.

At the practical level, treating the patient rather than the disease means considering what's important to the individual patient and keeping that in mind when deciding how to proceed. Consider the different effects a disease of the eye can have on an individual: The patient can have a symptom, such as pain; you may observe a sign such as a cupped optic nerve, a hemorrhage in the macula or high intraocular pressure; the disease may undermine the patient's visual ability, as registered by a specific metric such as visual acuity, contrast sensitivity or visual field; and/or the disease may undermine the person's ability to function. Of these, only two really matter to the patient: how the patient feels, and how well the patient is able to function. Patients don't care about signs. Their IOP or the fact that they have a hemorrhage on the optic nerve is totally immaterial to them. (Of course, they will care a great deal if you explain that these signs indicate progressive glaucoma that could lead to blindness; but the reason they will care is because you're now talking about their functionality and quality of life.)

I believe a doctor's primary job is not just to treat disease, but to care for how people feel and how they function. Patients may understand that something has improved because of your treatment—after all, you've undoubtedly told them so—but what they really want from you is improved

This article has no commercial sponsorship.

functionality and quality of life. That may or may not happen as a result of your treatment. Visual ability, as reflected by the patient's ability to read a Snellen chart, for example, doesn't necessarily translate to greater functionality or better quality of life.

This is one reason treating the patient is so different from treating the disease. The necessities of how each person has to function in order to get through the day vary widely; the functional needs of a professor may be quite different from the needs of a truck driver or a person managing a farm. As a result, some people's ability to function effectively in daily life may not correlate well with how that person does when taking the visual tests we typically conduct in the office.

Why We Focus on Disease

It's not a coincidence that physicians have ended up so focused on treating the disease instead of the patient. A number of factors have contributed to that trend:

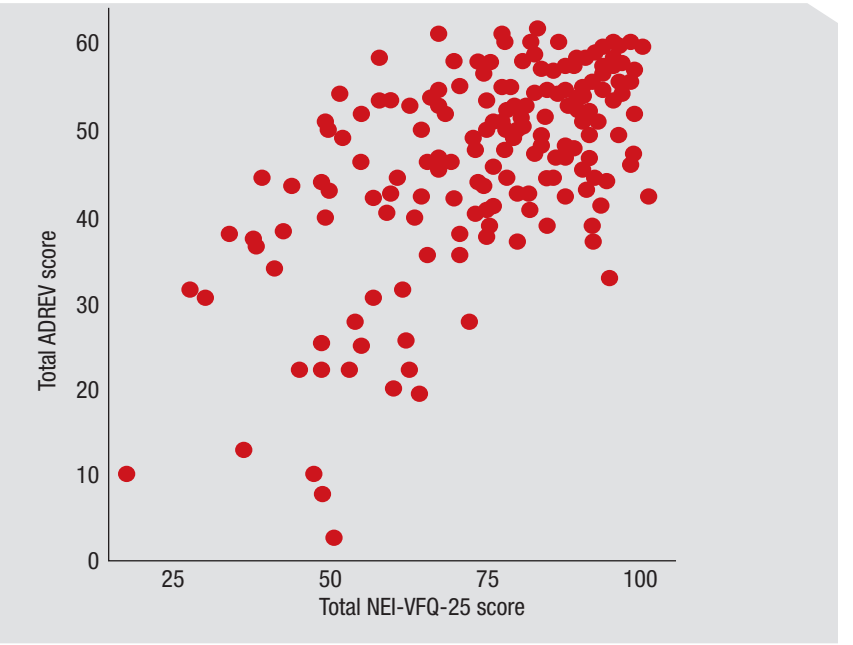
• ***We want to have a beneficial effect, and a change in a metric "proves" that we did.*** Having a beneficial effect is what we're being paid for. So if you take out a cataract, the patient's vision may go from 20/80 to 20/20, and you can say that you've made things better for the patient. However, the patient could end up with more glare than before, and that may be more important to some patients than improved acuity. So even though a standard metric says you've had a beneficial effect, you may also have changed the patient's vision in a way that lowers the patient's quality of life. The patient may end up quite unhappy.

In this situation the doctor can point to the metric that says the patient's vision is better, but doing so indicates a misunderstanding. The metric doesn't say you've made the patient better; the metric says you've made the patient's visual acuity better. It's not the same thing. (Of course, asking the right questions ahead of time might have revealed the patient's priorities and allowed the surgeon to modify his approach, preventing this unhappy outcome.)

• ***Finding out what matters to the patient isn't always easy.*** Another reason we tend to focus on the disease is that much of the information that can help us treat the whole patient comes from taking the history, which is by far the most difficult part of an evaluation. Patients often do not say what they really think. If you ask some glaucoma patients how they're feeling, they'll say they feel just great. You may see clear indications of visual difficulty, such as the patient having trouble finding the exam room chair or failing to respond when you hold out your hand to say hello. But if you comment on this, some patients will say "Oh no, that doesn't bother me." Meanwhile a quick check with the person who accompanied the patient to the exam may reveal that outside of the exam room the patient complains constantly about how miserable his visual disability is making him.

Of course, some patients present the opposite problem. I've had patients who complained that they were going blind every time they came in to see me, although I could never find a change in their measurements. I usually give the patient the benefit of the doubt and say that something must be going on; then I explain that I can't address it without being able to identify what it is. But I wouldn't dismiss the complaint. The patient's quality of life matters—not just the

Relationship Between Poor Vision and Quality of Life



Patients faced with the prospect of poor vision often assume their quality of life will drop dramatically as a result, but that is not necessarily true. This graph compares the ability to perform activities of daily living (y-axis), as measured by the individual's score on the Assessment of Disability Related to Vision scale (where 63 is the best possible score), to the individual's National Eye Institute Visual Function Questionnaire score.[6] The large point spread indicates that some people with limited vision have an excellent quality of life, while some who have very good vision do not. Challenging patients' assumptions can help to alleviate some of their fears and emotional suffering.

state of the disease—so if the patient is unhappy enough, I'd recommend that the patient get some other kind of assistance dealing with the symptoms she's experiencing.

• ***Our time with patients is more limited than ever.*** In the past, an ophthalmologist might have spent 15 to 30 minutes with a patient. Today most doctors have to move patients through their practices much more rapidly. If they don't, they can't generate enough return to cover their increasingly expensive office overhead. That encourages focusing on test results rather than the patient's functionality or quality of life.

I was recently in Germany, where I visited an office that pushed this idea to the limit. Patients went into a room with one table and one chair. The table has three instruments attached, intended to measure three things: IOP (without using drops), visual acuity and central corneal thickness. The doctor wanted those three pieces of information for every patient. So, the patient simply swung the chair around to have the three things tested. This allowed three billable tests to be done within five minutes.

Taking a history can be a more time-consuming way to earn reimbursement, but it's often more important in terms of revealing the patient's situation and real needs.

• ***Many doctors don't feel responsible for assisting the patient with his experience of the disease or disability.*** A physician might point out that a given patient is a grumpy old man, and say "What responsibility do I have for the fact the macular degeneration is making him miserable? I treated him with Lucentis and his vision improved from 20/60 to 20/40. I did a great job. It's not my fault that he's unhappy." My response would be that it IS our responsibility to do what we can to make patients less miserable—not just rein in their disease. Dr. Stetten, I think, would agree. Quality of life, without question, is the thing that matters most to our patients.

• ***Most physicians aren't trained to manage patient attitudes.*** This may be true, but it's not a reason to ignore the patient's problem. If you feel unqualified to help the patient deal with his anxiety, depression or trouble functioning, tell the patient that you can see he is having difficulty and suggest options for getting help from other sources.

It's important to remember that [our] measures are merely surrogates for the thing that really counts: how the patient is feeling and functioning.

Taken together, the factors listed above create a kind of perfect storm. They push doctors away from thinking about the patient's functionality and quality of life, shifting the focus toward just managing the disease. They encourage us to worry about objective measures such as a change in visual acuity, OCT or IOP. It's important to remember that those measures are merely surrogates for the thing that really counts: how the patient is feeling and functioning.

Deciding How to Proceed

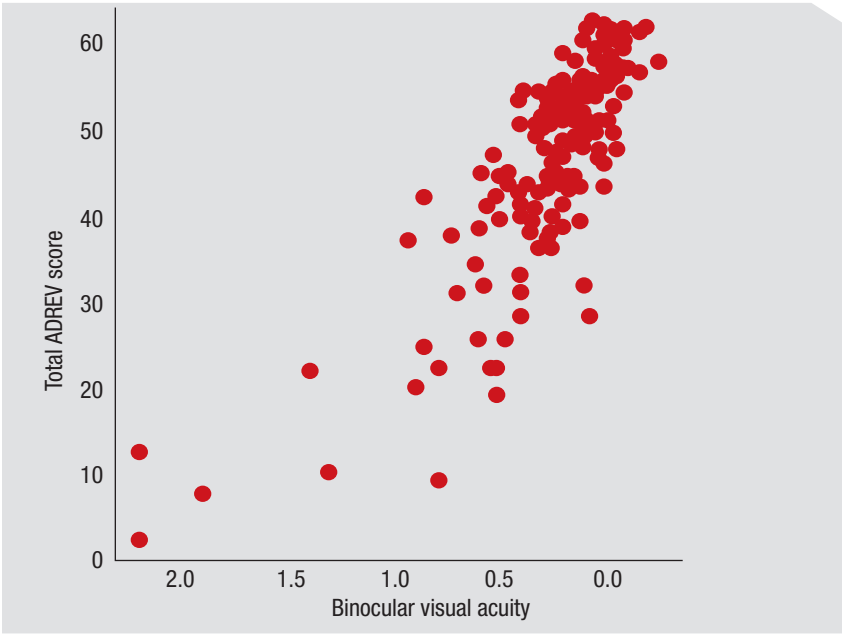
Clearly, vision impairment has an impact on functionality and quality of life. However, the impact that visual impairment has on any given individual depends on a number of factors that are within the physician's power to influence, including the patient's attitude and use of resources. To truly help our patients, we have to avoid letting our objective measures blind us to how the disease—and our treatment—are affecting the patient's functioning and quality of life.

When presented with a patient who is facing or managing vision loss, it's important for us to do a number of things:

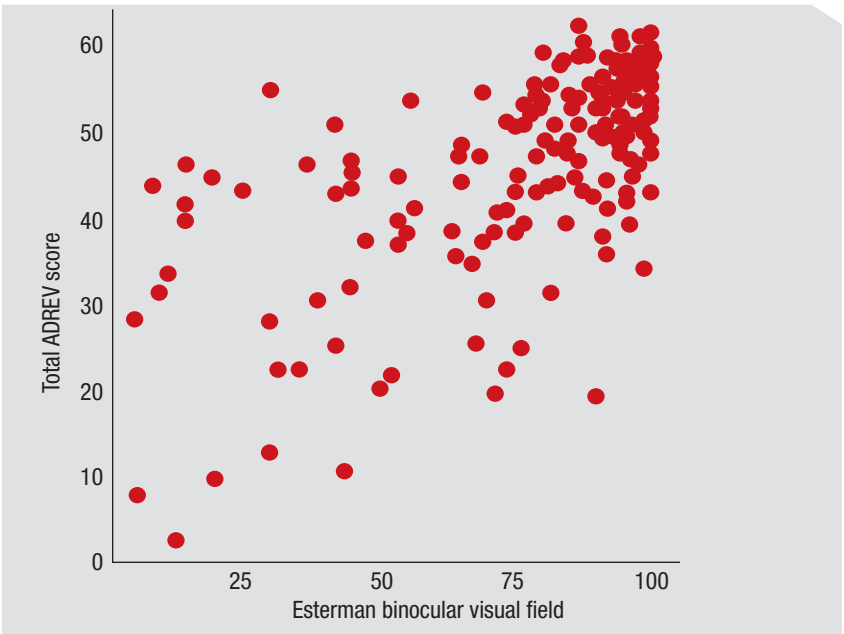
First, we need to evaluate how the disease is impacting the patient's quality of life and ability to function. Your evaluation may be based upon your observations and patient responses to questions, but there are also quantitative ways to assess this. I have a conflict of interest here (although not a financial one) because I've been involved in the creation of a clinical test for assessing the effect of visual loss on the ability to perform activities of daily living. The test, which involves detecting motion, reading signs, finding objects and navigating an obstacle course, takes 14 minutes (on average). It was evaluated in a recent study which found that the results correlated well with other measures used to evaluate people's changes in quality of life, including the National Eye Institute's Visual Functioning Questionnaire (NEI-VFQ-25).[2] At this point, such tests are not in wide use, so this is certainly not the standard of care. However, what this test reveals says a great deal about how the disease is affecting the patient's quality of life, so my hope is that a test of this type will eventually become just as standard as tests measuring visual acuity.

Second, once you've made your assessment—as subjective and imprecise as it may be—you have to decide whether the effect the disease is having on the patient is a significant issue for the patient. If it appears to be impacting the patient's quality of life and functionality, the patient may need help dealing with it. In some

Relationship Between Visual Acuity and Quality of Life



Relationship Between Visual Field and Quality of Life



Some types of vision difficulty are more likely to impact quality of life than others. The graphs above show that an individual's visual acuity has a much more pronounced impact on quality of life (as measured by the Assessment of Disability Related to Vision score) than the status of the individual's visual field.[6]

cases, it may tough to determine if the patient really does need help; but in other cases it will be clear that the patient is having trouble and needs counseling or some other form of assistance.

If it's clear that the patient would benefit from additional help, you have to decide whether this is something you can provide. In many cases I do try to counsel the patient myself. I'm not a trained counselor, but if this is a person I've been working with for a period of time and I believe she has trust and confidence in me, I may be able to help.

For example, I know a little about current low-vision aids. So I can say, "There are computer devices you can use to help you read; would you be comfortable going online to look at those?" Most of the time patients are happy to follow that lead. So in some cases it may not be necessary for me to refer the patient to another doctor or service.

If you're not comfortable trying to help directly, you have to decide what referral resources would be most appropriate. If the person is having trouble functioning because of reduced vision, you can suggest that she see a low-vision specialist you respect. It's great if you can honestly say, "I've sent other patients to Dr. Smith, and she is a wizard at helping people come to grips with this type of change. I don't have as much experience helping people with that as she does, and it's clear that this is really bothering you. So I'm going to send you to see her."

In other cases, it might be appropriate to refer the patient to a low-vision center; to a pastoral service, if the patient has strong religious beliefs; to a social service agency, where the patient might find help with issues such as getting to and from the doctor's office and managing his socioeconomic situation; or to an agency such as Associated Services for the Blind, where the person can get a battery of assessments, be evaluated for the use of a cane or guide dog and learn how to do laundry and other chores that might be challenging to manage with limited vision.

The Doctor's Perspective

In general, doctors do a better job of treating the patient—not just the disease—if they keep several things in mind:

• ***When making medical choices, remember that the goal is to maintain the patient's quality of life and functionality.*** In the case of managing glaucoma, this would include not overprescribing eye drops that may ultimately injure the cornea and degrade the person's vision. Remember: The goal is not to keep the patient's IOP low, or even to preserve the visual field. The goal is to maintain the patient's functionality and quality of life. If the treatment undermines that goal in the name of lowering IOP, you haven't done the patient a favor.

• ***Never underestimate the value of counseling for patients faced with vision loss.*** A randomized, controlled study conducted by Barry Rovner, MD, and William Tasman, MD, in the department of psychiatry at Jefferson Hospital for Neuroscience in Philadelphia, demonstrated the importance of counseling for patients with macular degeneration.[3] Two hundred sixty-five patients age 65 or older with pre-existing macular degeneration in one eye and a recent diagnosis of neovascular macular degeneration in the other eye were randomized into two groups, one of which received six sessions of problem-solving therapy in their homes; those in the other group received standard care. At two months, subjects who received counseling were half as likely to have a depressive disorder (11.6 percent vs. 23.2 percent, p=0.03). The counseling also reduced the likelihood that the patient had given up a valued activity (p=0.04). At six months, the beneficial effects had diminished, but subjects that received counseling were less likely to be suffering from persistent depression (p=0.04).

The message is clear: Getting counseling for patients in this kind of situation can make a significant difference in their quality of life.

• ***Stay informed about low-vision options.*** Providing this kind of information can be a great service to your patient. For example, very few of my patients realize that their computer can magnify type, take dictation and read text out loud. At the same time, resources such as low-vision doctors and social services may be totally outside of their experience, yet those resources could make an enormous difference in how well they cope with vision loss. However, in order to be a useful resource for your patients, you have to make an effort to stay up-to-date about the options in this area.

• ***Don't let the impact of new treatments overshadow the patient's situation.*** The medical profession has a long history of treating diseases rather than patients, and that tendency may be growing stronger over time, thanks our increasing ability to address disease. When Dr. Stetten saw his doctor about his macular degeneration, for example, there was no way to treat the disease. That's not the case today; now, we can improve vision in many patients we were powerless to treat in the past. Unfortunately, that may push us even further toward focusing on treating the disease rather than thinking about the patient as a whole.

No matter how miraculous your treatment may seem relative to what you could do in the past, the patient's functionality and quality of life is still the bottom line.

• ***Remember that vision loss impacts everyone differently.*** We usually assume that there is a close correlation between change in visual function and change in quality of life. There are indeed studies that show such an association—but the strength of that association is going to depend on the patient.

Years ago I reviewed a paper sent to me by a European journal about a group that had developed a quality-of-life survey for people who lived in Mali.[4] They hypothesized that quality-of-life surveys had to be culturally relevant in order to be valuable. Because there was no culturally relevant survey for the people who lived in Mali—most quality-of-life surveys were designed for people living in urbanized Western countries—they developed a survey they thought was appropriate and administered it.

I still clearly recall one of the graphs from that paper. Although there were some flaws in the data presentation, the graph showed something remarkable: The correlation between visual ability and quality of life changed depending on where in Mali you were living. If you lived in a city in Mali and your vision got worse, your quality of life got worse. If you lived in rural Mali, that correlation largely disappeared; there, if your vision deteriorated, your quality of life didn't change much. To me, that was an enormously important study. It provided a striking example of the reality that visual disability does not always correlate with a reduction in quality of life, and the presence or absence of that correlation can be affected by something as simple as where you live.

We can't assume that we know how a change in vision is going to affect a given patient. If vision drops from 20/20 to 20/40, some patients won't mind much; for others, it might make them suicidal and in need of counseling. So part of our job is to ask the patient how she feels about the current symptoms, as well as potential future symptoms such as loss of vision. It's absolutely imperative that we not assume we know what the patient is feeling. To care for the patient—not just treat the disease—we have to ask.

• ***Remember that different types***

of vision loss affect functionality to a greater or lesser extent. When managing glaucoma, loss of visual field is something we monitor on a regular basis. Yet studies have demonstrated that loss of visual acuity has a more profound effect on most types of functionality than loss of visual field does. The top chart on p. 43 shows the relationship between acuity and functionality as measured by the Assessment of Disability Related to Vision test. (This test measures a person's ability to do things such as read a sign at a distance and recognize faces; a higher score indicates better function.) The second chart shows the relationship between the subject's visual field and the same functionality score. The scatter is greater in the second chart because the correlation between loss of visual field and functionality is not as great.

There's one important caveat to trying to treat the whole patient: Taking your patient's situation and perspective into account does not mean that you should respond to a subjective complaint with medical or surgical treatment—unless you find measurable signs of a problem. If the patient's visual acuity has gone from 20/20 to 20/60, that's hard information, the kind that would stand up in court. If the patient says her vision is worse, but you can't document it in any way, doing a cataract extraction, for example, could backfire if the outcome isn't ideal. You could find yourself in the very difficult situation of trying to convince yourself (much less a court) that you acted properly on the basis of subjective information. You should still take the patient's complaint seriously, but if you can't find hard evidence to support it you could be on shaky ground responding with medications or surgery.

Getting the Big Picture

When you realize that one of your patients is struggling with vision loss—or fear of vision loss—taking these steps will help you get a clearer picture of what's happening:

• ***Ask about your patient's reaction to his vision impairment—and really listen to the answer.*** It's common for people in this situation to worry about losing their job and fear that they'll become dependent. Some people feel guilty, as if the vision loss was punishment for past errors; some become angry, asking "Why me?" Simply listening to the patient's concerns can do a lot to give the patient hope, and it will help to guide your choices for recommendations if it becomes clear that your patient needs assistance. Of course, you probably don't have the time to become your patient's emotional counselor, but the act of listening helps.

When faced with loss of vision, people often react with depression and despair. It can be helpful to provide a gentle reminder that, like many things in life, a setback can have positive consequences as well as negative ones.

• ***Inquire about the patient's lifestyle, especially in terms of how much time he spends alone.*** A patient who is isolated is likely to be in greater need of assistance, both psychological and physical. It may be that the caregiver who brings the person to your office isn't around at any other time. The patient may be very much alone and in need of human contact.

• ***Ask about how the people in the patient's circle of contacts are reacting to the patient's vision loss.*** If the family or friends of the patient are not being supportive, getting the patient outside assistance might be especially helpful. Even more important, close relationships such as living with a spouse are likely to change as a person loses vision and become more dependent. On the one hand, the spouse may feel validated in the marriage for the first time because she can do things for her husband that she wanted to do all along but was never able to do. He may be happy about it too. On the other hand, she may have her own life and feel stressed by his sudden dependence on her. This can lead to a relationship becoming hostile or breaking down.

Very few ophthalmologists are going to ask a patient with macular degeneration who is not responding well to treatment, "How is your marriage going? Is it still OK?" But it may be a very important question to ask, because it may be the opening the patient needs to admit that his marriage is in trouble. The ophthalmologist can say, "I'm not the best person to counsel you about that, but it's not rare that patients have difficulties when one of them loses vision. It's nothing to be ashamed of. You may want to bring that up with your primary care physician, or seek some kind of counseling. Getting help managing this change could make a big difference." Just getting that far could go a long way toward helping your patient.

Helping Patients Manage

Although we may not have the time or skills to provide professional counseling, a few simple strategies can go a long way toward improving

your patient's quality of life.

• ***Provide encouragement, hope and perspective.*** When faced with loss of vision, people often react with depression and despair. It can be helpful to provide a gentle reminder that, like many things in life, a setback can have positive consequences as well as negative ones. It's also worth reminding patients that situations we encounter—positive or negative—seldom have the huge impact we expect them to. Achievements we thought would make the rest of our life blissful often fall short, and disasters we thought we couldn't possibly survive turn out to be manageable—and sometimes even produce unexpected benefits.

Several years ago I spent some time interviewing patients who had significant visual loss. One of the things I discovered was that individuals experiencing loss of vision tend to be very afraid of becoming dependent on others. However, they didn't usually end up becoming as dependent as they thought they would. Most people who lose vision quickly discover that there are all kinds of ways to cope that they didn't know about. Also, as the graph on p. 43 shows, some individuals lose a lot of their vision and still manage to have a good quality of life. Making your patients aware of this may help them avoid despair and depression.

• ***Sharing a story or two may help some patients.*** I've known individuals who lost most of their vision but still were cheerful and accomplishing impressive things. One woman who was nearly blind informed me that she had just graduated from law school, first in her class. A woman psychotherapist in Hong Kong who lost her sight at age 8 as a result of Stevens-Johnson syndrome has written that her blindness ended up becoming a blessing. "There are lots of challenges, but the benefits are greater," she wrote. "I experience blessings around me every day and everywhere even though I can't see. My blindness opened my eyes in a different way."[5] On the other hand, I've seen people with minimal visual disability who labeled themselves "disabled" and gave up on life.

Handled in a positive way, a setback in vision can end up leading to positive changes in a person's life. That's the kind of attitude that needs to be encouraged, and sharing stories like these can sometimes help.

• ***Consider having the patient speak to another patient who has done well.*** If another patient you know well has been in the same situation—and is a good communicator—this can be helpful. However, it's important to check with the other individual first and make sure he's willing to share his experience before putting the patient in touch with him.

• ***Remind your patient that attitude can make a big difference in how well things turn out.*** Even though quality of life and functionality are closely related, they're not the same thing. Quality of life is a feeling we have about our functionality. How do I feel about the fact that it's becoming hard to drive? For some people, no longer being able to drive would be horrifying, resulting in a devastating decrease in their quality of life. Others wouldn't care that much; it might be a great excuse to get their daughter to drive them around, which would make them happy. So the same loss of functionality can have a very different impact on quality of life for different individuals.

Loss of sight is a challenge, and like any challenge, how you cope with it will depend in large measure on the way you frame the situation in your mind. What people sometimes forget is that the perspective we have about our situation is always under our control. That's why it's worth reminding your patient that making the effort to look for potential positives in a difficult situation caused by vision loss can remove some of the fear and difficulty. Then, despite some loss of functionality, the impact on the patient's quality of life won't be as great.

Moving in the Right Direction

Fortunately, there is now a growing interest in treating the patient as well as the disease. This is especially evident in some areas such as cancer treatment. I often see advertisements inviting patients to choose a particular cancer treatment center because the doctors "focus on the whole patient"; doctors at that center are willing to consider alternate treatments such as meditation and options beyond chemotherapy and radiation. I think that's a step in the right direction. It's saying, "You are not a cancer—you are a person who has cancer." We need to move in the same direction: "You are not a case of glaucoma. You are a person I'm trying to help who happens to have glaucoma."

Seeing our goal as treating the patient—not just the disease—is a simple change in perspective. But it's a change that can make a world of difference; it can change how effective we are at helping our patients to end up with happier and more effective lives. REVIEW

Dr. Spaeth is the Louis J. Esposito Research Professor at Wills Eye Hospital/Jefferson Medical College in Philadelphia.

1. Stetten D. Coping with Blindness. N Engl J Med 1981; 305:458-460.
2. Wei H, Sawchyn AK, Myers JS, Katz LJ, Moster MR, Wizov SS, Steele M, Lo D, Spaeth GL. A clinical method to assess the effect of visual loss on the ability to perform activities of daily living. Br J Ophthalmol 2012;96:5:735-41.
3. Rovner BW, Casten RJ, Hegel MT, Leiby BE, Tasman WS. Preventing depression in age-related macular degeneration. Arch Gen Psychiatry 2007;64:8:886-92.
4. Schémann JF, Leplège A, Keita T, Resnikoff S. From visual function deficiency to handicap: measuring visual handicap in Mali. Ophthalmic Epidemiol 2002;9:2:133-48.
5. South China Morning Post, February 2, 2015, p. 20–22.
6. Altangerel U, Spaeth GL, Steinmann WC. Assessment of function related to vision (AFREV). Ophthalmic Epidemiol 2006;13:1:67-80.

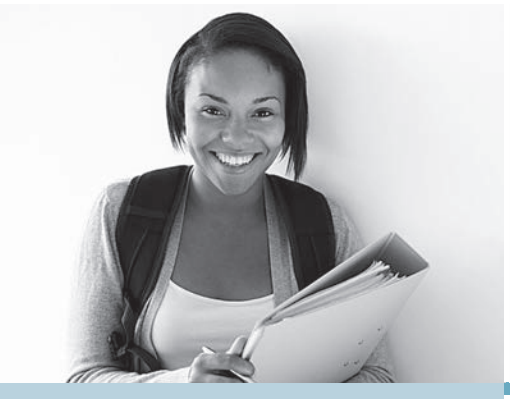


The Rick Bay Foundation

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 are awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and are 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

(Contributions are tax-deductible in accordance with section 170 of the Internal Revenue Code.)

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

Working Magic with Pharmacokinetics

How increasing the absorption, bioavailability and/or retention of a drug can result in better efficacy without greater side effects.

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

In one of our recent columns, we put forth a primer—or more accurately, a refresher—on the principles of pharmacokinetics as they relate to ocular drug therapies. *(See Therapeutic Topics, October 2015)* In that article, we described the specifics of drug design and formulation that focus on balancing therapeutic dose and duration with adverse effects and cost optimization. Although the eye has the unique advantage of access, and topicals account for about 90 percent of all aqueous ophthalmic formulations,[1] a significant barrier to ocular drug delivery is posed by the pre-corneal tear film, the corneal epithelium, the stroma and the conjunctiva. The combined action of these tissues and cellular constructs can render topical ocular drug delivery methods inefficient or ineffectual, and often necessitates higher drug concentrations, increased dosing frequency or both.

This central challenge for ophthalmic drug developers is being addressed through a number of chemical and physical sleight-of-hand strategies to improve the absorption, bioavailability or retention of therapeutics. By enhancing the amount of drug that can reach its target, or the duration of the drug at the target site, we use pharmacokinetic principles to achieve greater efficacy without onerous dosing regimens or amplified side effects. This month, we'll describe several novel strategies for increasing drug concentrations, enhancing drug penetration and extending drug retention.

Increasing Drug Concentrations

It's well-known that the small, hydrophilic molecules are generally the best therapeutics.[2] But how do we deal with hydrophobic drug candidates with good *in vitro* profiles? Enhancing the solubility of any drug allows for greater drug loading, resulting in more drug being delivered. While a potential drug candidate with a hydrophobic character may be better if corneal penetration is part of the goal, limits on aqueous solubility will affect the ability of the drug to achieve sufficient therapeutic concentrations in aqueous.[3] An example of this is cyclosporine, a drug used to treat dry eye. One promising approach to this problem is the use of water-soluble compounds called hydrotropes, designed to enhance the aqueous solubility of hydrophobic compounds. Compounds demonstrating hydrotropic properties include caffeine; nicotinamide; urea; cyclodextrins; N,N-diethyl-nicotinamide; and N,N-dimethylbenzamide. The solubility enhancement of these compounds has ranged from relatively modest to upwards of 10,000-fold. These hydrotropes have only been tested on a limited set of hydrophobic drugs, but results are promising.[2,3]

Innovative colloidal dosage forms for ocular drug delivery also offer solutions to drug solubility. In particular, polymeric nanoparticles, nanomicelles, liposomes and niosomes are known to increase drug solubility. These nanostructures, which range in particle size from 1 to 1,000 nm, capture the poorly soluble drug, allowing for improved distribution within an aqueous solution. Biodegradable polymeric nanoparticles take either the form of nanospheres, within which the parent drug is dispersed in a polymeric matrix or is otherwise adsorbed to the surface of the nanosphere; or the form of a nanocapsule, within which the parent drug is dissolved and surrounded by the polymeric membrane.[4] These

This article has no commercial sponsorship.

nanoparticle carriers are then dispersed within a water-based vehicle.[5] Micelles are nanoscale phospholipid balloons that form when molecules possessing both hydrophilic and hydrophobic groups are exposed to a suitable solvent and the molecules orient with the hydrophilic portions orienting outwards, forming a hydrophobic core, which can also then encapsulate a hydrophobic parent drug.[6] Liposomes form nanovesicles capable of entrapping both hydrophilic and hydrophobic drugs by virtue of the molecule's inner hydrophilic core and peripheral hydrophobic compartments.[5] Niosomes are vesicles composed of non-ionic surfactants that are structurally and functionally similar to liposomes.

Enhancing Access

The two primary strategies for improving ocular drug delivery are developing prodrugs and adding penetration-enhancing agents that modify the ocular surface. Enhancing penetration improves site-specificity, consequently increasing the amount of drug that reaches the target tissue while decreasing toxicity.

Prodrugs are commonly used to enhance drug penetration, and are inactive or less-active derivatives of active drug molecules that are converted to the active form *in vivo*. The concept of prodrugs isn't new, although development of prodrugs has surged recently. In the first decade of this century, prodrugs accounted for nearly 20 percent of approved new chemical entities.[7] Approved ophthalmic prodrugs are currently in use for managing intraocular pressure and open-angle glaucoma (e.g., latanoprost, bimatoprost, travoprost and unoprostone isopropyl), as well as for managing ocular pain and inflammation following ocular surgery (e.g., nepafenac). These topically administered ophthalmic prodrugs take advantage of lipophilic pro-moieties to enhance penetration of the corneal barrier. While this remains a successful strategy, a new generation of ocular prodrugs that seeks greater tissue specificity by targeting cell-specific or tissue-specific endogenous enzymes or transporters is on the horizon.[8] Examples of this shift in pro-drug strategy are compounds that target peptide or amino acid transporters to facilitate uptake of prodrug variants of antiviral drugs such as acyclovir and gancyclovir.[6]

By comparing tear-film breakup, caking, blurring and comfort scores, it's possible to determine an optimal viscosity (usually about 70 to 135 centipoise) for each drop formulation.

Another method for enhancing ocular penetration is to add enhancers that directly modify the physical barriers of the ocular surface; for example, by disrupting tight cell junctions between superficial epithelial cells, or by partially solubilizing and removing cell membrane phospholipids on the ocular surface.[9,10] These enhancers can be effective at promoting paracellular and transcellular transport of drugs, but modifying physical barriers can have consequences. Eye irritation and cellular damage have been associated with early generation penetration-enhancing agents, so the current focus is on penetration enhancers that act with minimal toxicity, maximal comfort and are compatible with formulation ingredients. These agents are also designed to act at low concentrations, with a fast yet reversible onset of action.[11] Examples include Gelucire 44/14 (Gattefossé, Lyon, France), an amphiphilic molecule, and cyclodextrin, a compound with multiple pharmacokinetic-enhancement effects.[11,12] It's thought that the amphiphilic character of Gelucire 44/14 allows it to act as a surfactant, promoting both transcellular and paracellular transport by its actions on cell membranes and tight junctions.[11] Cyclodextrin has been shown to interact with the sterols in cell membranes, swapping a cholesterol in exchange for a drug held within its hydrophobic core.[12] These enhancers have garnered the interest of pharma due to their favorable tolerability and ability to solubilize drugs.[1,11,12]

Extending Drug Duration

Retention strategies are continually evolving as drug developers seek to improve the bioavailability of ophthalmic drugs by extending the duration of the drug. One approach we've tested in pre-clinical studies is adding lysine homo-polymers, compounds that can adhere to the epithelial surface and to the drug molecule, acting as tethers to keep drug molecules resident at the surface. More often, residence time is prolonged through the use of agents such as hydroxy propyl methyl cellulose to increase drop viscosity, and by the use of drug carriers that can act as drug reservoirs.

Raising the viscosity of an ocular drug-delivery formulation helps to slow the rapid dilution and drainage caused by tear-film turnover. This approach must be weighed against a few distinct disadvantages, however: Highly viscous solutions can cause transient blurring of vision upon instillation, and are subject to imprecise dosing. An alternative approach involves gelling systems that undergo a phase transition from a liquid to a gel upon exposure to certain physiological conditions, such as temperature or pH. These systems can be delivered with the precision of a

drop, but retain the ability of viscosity-enhanced delivery systems to retard the dilution and drainage of the precorneal tear film. At the same time, they also minimize gels' transient impact on vision. Other polymers tested for use in the eye are designed to interact with native mucins. The residence time of formulations using these muco-adhesive polymers is governed by the turnover rate of the tear mucin layer, which is slower than that of the bulk tear film.[1,13]

In addition to properties that promote solubility and drug penetration, some nanoparticle, liposome, nanoemulsion and dendrimer formulations also prolong duration. As a drug is attached to the matrix or encapsulated within a nanoparticle delivery system, the system protects the drug from degradation and slows diffusion into the bulk solution, prolonging overall residence time.[14] Drug release is then controlled by the degradation rate of the delivery system, the solubility of the drug and the diffusion of the drug within the nanoparticle delivery system.[15]

Punctal plugs can be considered one of the simplest pharmacokinetic-modifying strategies, slowing tear drainage and prolonging the action of artificial tears by physical occlusion of the lacrimal drainage. More recently, plugs have become important sustained-release delivery systems. The plug is usually coated to render all sides but the head impermeable to the drug and tear fluid. Drug diffuses over time into the tear film from the head of the device.[16] The combination of depot drug delivery and slowing of tear drainage provides a one-two punch of therapeutic enhancement. Trials are under way to evaluate the use of punctal plugs for the extended release of travoprost or latanoprost to treat glaucoma.

An approach similar to the punctal plug is the intracanalicular depot. This device slows drainage while at the same time delivering a sustained dosing of dexamethasone (the approach of Ocular Therapeutix), and may also work with other drugs. The steroid depot has shown promise as a treatment for chronic allergic conjunctivitis, and is being tested for treatment of dry eye and ocular inflammation as well.[17]

As the progression of polymers to be evaluated for their suitability as prolonged-release drug delivery systems marches on, an alternative—drug-loaded ocular inserts as delivery modalities—is also on the rise. One polymer unique in its combination of qualities is chitosan. Chitosan is a biodegradable, biocompatible and nontoxic natural carbohydrate polymer that has mucoadhesive properties. Chitosan-based ocular inserts enhance precorneal residence time of the co-applied drug, with promising initial results in studies with various drugs.[18]

Biodegradable and non-biodegradable implants are emerging as a method for effective long-term delivery of drug to the posterior chamber. As with intravitreal injections, the approach, while invasive, avoids several of the ocular barriers to drug delivery while enabling sustained-release kinetics over a period of years. In 2014, Iluvien (Alimera Sciences) was granted Food and Drug Administration approval as an injectable intravitreal device for treatment of diabetic macular edema in patients who have previously been treated with a course of corticosteroids and did not have a clinically significant rise in IOP. Iluvien is a non-biodegradable, cylindrical polyimide implant that releases 0.23 to 0.45 µg/day of fluocinolone acetonide for 18 to 36 months. The device is small enough to be implanted into the back of the eye using a 25-gauge needle. Iluvien was developed using the Durasert technology platform (pSivida), which also is currently being investigated by Pfizer for a fully bioerodible, sustained-release delivery system for latanoprost.

The last two decades have seen remarkable innovation in the development of ophthalmic drug delivery systems. Improvements have been driven in large part by considerations of patient compliance, as technologies that increase drug concentrations, penetration and duration should result in reduced dosing requirements and improved efficacy. Research under way in this area pushes boundaries and involves contributions from clinicians, pharmacologists and materials scientists. As this consortium works its magic, we can expect to see a host of new therapeutic modalities materialize in the near future. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School, emeritus surgeon at the Massachusetts Eye and Ear Infirmary and chief scientific officer at Ora Inc. Dr. McLaughlin is a senior regulatory writer at Ora.

1. Morrison PW, Khutoryanskiy VV. Advances in ophthalmic drug delivery. Ther Deliv 2014;5:12:1297-315.
2. Lipinski C, Hopkins A. Navigating chemical space for biology and medicine. Nature 2004;432:7019:855-61.
3. Kim JY, Kim S, Papp M, et al. Hydrotropic solubilisation of poorly water-soluble drugs. J Pharm Sci 2010;99:9:3953-65.
4. Almeida H, Amaral MH, Lobão P, et al. Applications of polymeric and lipid nanoparticles in ophthalmic pharmaceutical formulations. J Pharm Pharm Sci 2014;17:3:278-93.
5. Cholkar K, Patel SP, Vadlapudi AD, et al. Novel strategies for anterior segment ocular drug delivery. J Ocul Pharmacol Ther 2013;29:2:106-23.
6. Cholkar K, Patel A, Vadlapudi AD, et al. Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. Recent Pat Nanomed 2012;2:2:82-95.
7. Stella VJ. Prodrugs: Some thoughts and current issues. J Pharm Sci 2010;99:12:4755-65.
8. Huttunen KM, Raunio H, Rautio J. Prodrugs—from serendipity to rational design. Pharmacol Rev 2011;63:3:750-71.
9. Kaur IP, Smitha R. Penetration enhancers and ocular bioadhesives: Two new avenues for ophthalmic drug delivery. Drug Dev Ind Pharm 2002;28:4:353-69.
10. Burgalassi S, Chetoni P, Monti D, et al. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. Toxicol Lett 2001;122:1:1-8.
11. Liu R, Liu Z, Zhang C, et al. Gelucire44/14 as a novel absorption enhancer for drugs with different hydrophilicities: In vitro and in vivo improvement on transcorneal permeation. J Pharm Sci 2011;100:8:3186-95.
12. Adelli GR, Balguri SP, Majumdar S. Effect of cyclodextrins on morphology and barrier characteristics of isolated rabbit corneas. AAPS PharmSciTech 2015;16:1220-1226.
13. Agrawal AK, Das M, Jain S. In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert Opin Drug Deliv 2012;9:4:383-402.
14. Kim NJ, Harris A, Gerber A, et al. Nanotechnology and glaucoma: A review of the potential implications of glaucoma nanomedicine. Br J Ophthalmol 2014;98:4:427-31.
15. Mudshinge SR, Deore AB, Patil S, et al. Nanoparticles: Emerging carriers for drug delivery. Saudi Pharm J 2011;19:3:129-41.
16. Gooch N, Molokhia SA, Condie R, et al. Ocular drug delivery for glaucoma management. Pharmaceutics 2012;4:1:197-211.
17. Walters T, Endl M, Elmer TR, et al. Dexamethasone punctum plug for the treatment of ocular inflammation and pain after cataract surgery. J Cataract Refract Surg 2015 (in press).
18. Franca JR, Foureaux G, Fuscaldi LL, et al. Bimatoprost-loaded ocular inserts as sustained release drug delivery systems for glaucoma treatment: In vitro and in vivo evaluation. PLoS One 2014;9:4:e95461.

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.

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 and forums.

www.reviewofophthalmology.com

Jobson Medical Information LLC
The *Review* Group

How to Stay Out Of the Courtroom

Complications will happen, but how you respond to them can make the difference between a happy patient and a lawsuit.

C. Gregory Tiemeier, Denver

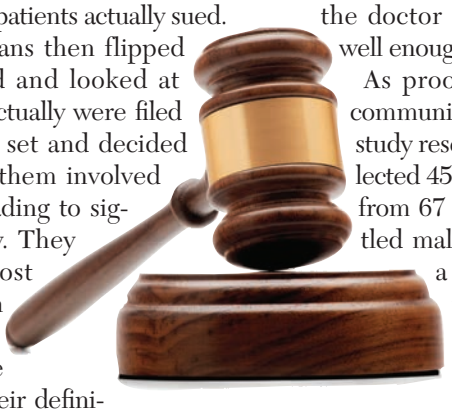
As a defense attorney, I often tell clients who are being sued for malpractice that just being in a courtroom means they've already lost: They lose time from their practice and have to deal with the stress of defending themselves in court. Because of this, the best malpractice defense is to not get sued in the first place. In this article, I'll share my advice on how to decrease the odds of a lawsuit, based on 30 years of experience with malpractice litigation, much of it in the realm of refractive surgery.

Being Skilled Isn't Enough

One of the unfortunate facts of malpractice lawsuits is that just being a good surgeon won't protect you from being sued. This has been borne out by personal experience as well as the scientific literature.

In 1991, in *The New England Journal of Medicine*, a study was published that looked at surgeries and resulting malpractice claims.[1] In the study, a panel of physicians from Harvard Medical School studied 31,429 patient charts and tried to determine which of the charts contained evidence of significant injury that was caused by negligence of a health-care provider. They then separated out those charts with evidence of negligence and looked to see if any of those patients filed a suit in that jurisdiction. They found that, in those cases where they thought there was negligence leading to injury, only 2.8 percent of patients actually sued.

The physicians then flipped things around and looked at lawsuits that actually were filed from the data set and decided how many of them involved negligence leading to significant injury. They found that most of the events in which claims were made didn't meet their definition of negligence. So, in the end, it seems most patients who are victims of negligence don't file malpractice lawsuits and most of the patients who file lawsuits aren't victims of negligence. The take-home message for physicians, then, is that being a good doctor and practicing good medicine won't necessarily protect you from being sued.



Communication Matters

So, if surgeon skill isn't at the heart of malpractice lawsuits, what is? After defending ophthalmologists in refractive surgery lawsuits for many years, I've found that in these cases, more often than not, the suing patient feels the doctor didn't communicate well enough.

As proof of how important communication can be, in one study researchers randomly selected 45 plaintiffs' depositions from 67 depositions from settled malpractice suits against a large metropolitan medical center and tried to answer the question of why the patients sued. In 71 percent of the cases, the researchers identified problematic relationship issues, such as deserting the patient, devaluing the patient's and/or the family's views and delivering information poorly.[2] With these findings in mind, here are some tips for communication that can help you avoid a lawsuit:

• ***Preop discussions.*** In many lawsuits, patients don't feel that the

This article has no commercial sponsorship.

surgeon is on their side after a complication occurs. You can help avoid this by starting the doctor-patient bonding process early on when you present the informed consent. Don't just give the consent form to the patient and blurt out, "Let me know if you have any questions." This is like a high-priced tour guide meeting you in a foreign country, shoving some maps in your hand and leaving with a quick "Have fun." Instead, guide the patient through the form, explaining what the surgery entails, what the likely complications are and, if any complications occur, identify which ones you can fix and which ones would be more challenging. Don't treat informed consent as a legal technicality you have to get out of the way, but see it as an opportunity to begin strengthening the doctor-patient relationship. Also, be sure to use procedure-specific consent forms and give the patient the forms as soon as you start talking about the procedure, not on the day of the surgery.

• ***After a complication.*** Though good preop communication is important, how you deal with a patient who has had an adverse event or complication is even more so.

First, contact your insurer and have someone walk you through how to have a conversation with the patient. Then, meet with the patient; don't try to duck him. Unfortunately, I see this often: Once there's a complication, the doctor doesn't want to see the patient as much. This might be a natural reaction, since a surgeon feels he's very competent and may not want to deal with direct evidence of whatever it is that he did, but it's always counterproductive in terms of avoiding a lawsuit.

When you meet with the patient, don't do it in your exam lane. Instead, sit next to him in a conference room or at a lunchroom table, put the chart in front of you and go over what happened. If you have an idea about what went wrong, tell him. If you don't know, discuss what you think the possibilities are. And, most important: Tell him what you're going to do about it. I've seen many lawsuits in which the surgeon told me that there was nothing to tell the patient because he was going to wait three months and then reoperate. "Did you tell the patient that was one of the options?" I always ask. To which the surgeon usually replies, "No, I just told the patient, 'Come back in three months.' " The main message you should be conveying to the patient is that you're on his side and that you're companions in this, not adversaries. It will be you and him against the complication.

During your postop conversations with a patient who has a problem, be sure to ask, "How are you doing with earning income at the moment, is this causing a problem?" The financial question is relevant because some patients, a truck driver for example, may lose their jobs if they don't see 20/40 or better in at least one eye. In fact, the first multimillion dollar LASIK lawsuit was brought by an airline pilot who was unable to land commercial jets due to glare at night.

I'm not saying you need to cover the patient's expenses, but sometimes all he needs is a note from a doctor that he can't work for the next week, or something that can trigger his disability coverage. If you don't ask the question you won't know the answer.

There's also an emotional aspect you should address. Ask, "Are you handling this OK?" If the patient breaks down crying, it's a good idea to spend 15 minutes or so with him or her, saying such encouraging things as, "Don't despair—there's hope. We'll work through this together."

• ***Dealing with second opinions.*** Communication issues often send patients running to another physician for another opinion, which can result in a lawsuit, depending on what that physician says. In my experience, most of the cases I get are a result of a comment that was made by another doctor. In the second study discussed earlier, for example, 54 percent of a sub-group of patients who sued said a health-care professional had suggested there was some maloccurence.[2]

One thing you must be aware of is that there appears to be a lot of vitriol between physicians who compete in the same area, and I'm seeing more incidents of competitors using lawsuits against each other as a marketing tool. For example, I'm aware of one case in which the second-opinion doctor erroneously told the patient he had suffered malpractice by a surgeon's procedure, even though the procedure hadn't even been performed. In this type of environment, if communication breaks down and an angry patient goes to a competitor for a second opinion, you could be heading for a lawsuit.

To short-circuit this possibility, you might want to say to the patient, "Maybe you'd like to talk to another doctor about this," and then suggest someone. This way, even though it may hurt to suggest the patient get a second opinion, at least you're exercising some control. By doing this, you can steer the patient toward someone you know will give an intelligent, independent opinion, and won't try to steal the patient and turn this into a lawsuit that he can use against you.

In refractive surgery as in other specialties, complications are inevitable, even for a skilled surgeon. However, when it comes to avoiding a lawsuit, the fact there was a complication is much less important than how you deal with it. REVIEW

Mr. Tiemeier is a partner in the law practice of Tiemeier and Stich in Denver.

1. Localio AR, Lawthers AG, Brennan TA, et al. Relation between malpractice claims and adverse events due to negligence — results of the harvard medical practice study III. N Engl J Med 1991;325:245-251.
2. Beckman HB, Markakis KM, Suchman AL, Frankel RM. The doctor-patient relationship and malpractice. Lessons from plaintiff depositions. Arch Intern Med 1994;154:12:1365-70.

Prevention of CME After Cataract Surgery

Researchers evaluating the optimum medical strategy to prevent cystoid macular edema after cataract surgery concluded that topical nonsteroidal anti-inflammatory drugs significantly reduced the odds of developing CME, as compared to topical corticosteroids, in non-diabetic and mixed-population groups. A combination of topical NSAIDs and corticosteroids reduced the odds of developing CME in nondiabetic and diabetic patients, as compared to topical corticosteroids.

Cochrane, Medline and Embase databases were searched to identify the eligible randomized clinical trials (comparing medical strategies to prevent CME after uncomplicated cataract surgery in non-diabetic and diabetic patients) for systematic review and meta-analysis. The data were extracted independently by two authors. The quality of individual RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias and Delphi criteria.

The primary outcome measured was the odds of developing CME within three months postop. Secondary outcome measures were foveal thickness, macular volume and corrected distance visual acuity change as compared to baseline, also within three months postop. Of the 30 identified trials included in the systematic review, 17 reported incidence rates. Eleven trials included only non-diabetic patients, while 7 trials included only diabetic patients. There were 12 other trials that included patients with and without diabetes or did not report the incidence of diabetes in the study population; these trials were clustered and are referred to as "mixed populations" for the purpose of reporting results.

Topical NSAIDs significantly reduced the odds of developing CME as compared to topical corticosteroids in non-diabetic populations (odds ratio: 0.11; 95 percent confidence interval, 0.03 to 0.37) and mixed populations (OR: 0.05; 95 percent CI, 0.02 to 0.11). A combination of topical corticosteroids and NSAIDs significantly reduced the odds of developing CME as compared to topical corticosteroids alone in non-diabetic (OR: 0.21; 95 percent CI, 0.10 to 0.44) and diabetic patients (OR: 0.17; 95 percent CI, 0.05 to 0.5). Intravitreal corticosteroid or anti-VEGF injections did not show any additional benefit in diabetic subjects.

Am J Ophthalmol 2015;160:5:968-981.

Wielders L, Lambermont V, Schouten J, Van den Biggelaar F, et al.

MIVI-TRUST Trials Patients Report Visual Function Improvement

Results of the Microplasmin for Intravitreous Injection-Traction Release Without Surgical Treatment (MIVI-TRUST) trials suggest that ocriplasmin produces clinically meaningful improvement in patient-reported visual function in symptomatic vitromacular adhesion and vitromacular traction.

To determine the impact of intravitreal ocriplasmin on patient-reported visual function, researchers used the 25-item National Eye Institute Visual Function Questionnaire during a six-month follow-up in patients with symptomatic VMA. Patients were recruited to two multicenter, randomized clinical trials at clinic-based centers in the United States and Europe. A total of 652 patients with symptomatic VMA/VMT, including when associated with a macular hole 400 µm or smaller, were studied. Analysis was by intent-to-treat population.

The patients were randomly assigned (2:1 in Group 1, 3:1 in Group 2) to receive a single intravitreal injection of ocriplasmin 125 µm or placebo. The NEI VFG-25 was administered at baseline and six months following the ocriplasmin injection. The mean changes between baseline and six-month follow-up NEI VFQ-25 composite and subscale scores and the proportion of patients with a clinically meaningful change (≥five points) in scores were measured.

Across the two studies, 464 patients received ocriplasmin and 188 received placebo. At six months, the ocriplas-

min group reported greater mean improvements from baseline in the NEI VFQ-25 composite score than the placebo group (mean change, 3.4 vs. 0.7, p=0.005). Improvements were also noted in subscale scores, with the following respective mean changes for the ocriplasmin vs. placebo groups: vision-related dependency, 1.7 vs. -2.1 (p=0.009); driving difficulty, 2.7 vs. -1.5 (p=0.03); distance vision activities, 4.1 vs. 0.8 (p=0.03); and general vision, 6.1 vs. 2.1 (p=0.003). A higher proportion of the ocriplasmin group had a clinically meaningful (≥five point) improvement in NEI VFQ-25 composite score from baseline than placebo group (36 percent vs. 27.2 percent, p=0.03). Fewer ocriplasmin-treated patients had a clinically meaningful worsening in their visual function than the placebo group (15 percent vs. 24.3 percent, p=0.005). Changes in NEI VFQ-25 composite score and various subscale scores were observed in ocriplasmin-treated patients who achieved VMA resolution at day 28.

The article's authors disclose financial interest in the products and/or companies referenced in the article.

JAMA Ophthalmol 2015;133:9:997-1004.

Varma R, Haller J, Kaiser P.

Combining Glaucoma Screening Technologies for Better Detection

A multi-institutional research team has determined that a multivariable model including GDx-TSNIT (scanning laser polarimetry temporal-superior-nasal-inferior-temporal), number of abnormal points (NAP) on frequency doubling technology (FTC), and the interaction GDx-TSNIT x NAP-FDT provides the best glaucoma prediction with all other multivariable and univariable models. Combining the FDT C-20-5 screening protocol and scanning laser polarimetry with variable corneal compensation (GDx-VCC) improves glaucoma detection compared with using GDx or FDT alone.

Normal (n=110) and glaucomatous (n=114) subjects were tested with the FDT C-20-5 screening protocol and the GDx-VCC. The discriminating ability was testing for each device individually and for both devices combined using GDx-NFI (nerve fiber indicator), GDx-TSNIT, number of missed points FDT and normal or abnormal FDT. Measures of discrimination included sensitivity, specificity, area under the curve (AUC), Akaike's information criterion (AIC) and prediction confidence interval lengths.

For detecting glaucoma severity, the multivariable model resulting from the combinations of GDx-TSNIT, NAP-FDT and the interaction GDx-TSNIT x NAP-FDT (AIC: 88.28, AUC: 0.959, sensitivity: 94.6 percent, specificity: 89.5 percent) outperformed the best single-variable model provided by GDx-NFI (AIC: 120.88, AUC: 0.914, sensitivity: 87.8 percent, specificity: 84.2 percent). The multivariable model combining GDx-TSNIT, NAP-FDT and interaction GDx-TSNIT x NAP-FDT consistently provided better discriminating abilities for detecting early, moderate and severe glaucoma than the best single-variable models.

J Glaucoma 2015;24:561-567.

Mwanza J, Warrn J, Hochberg J, Budenz D, et al.

Incidence of Late-Stage AMD in American Whites

Population health researchers from London have concluded that estimating age-related macular degeneration incidence from prevalence allows for a better characterization at older ages and by AMD subtype where longitudinal data from incidence studies are limited.

The researchers did a systematic review and meta-analysis of prospective cohort studies of AMD incidence in populations of white European ancestry published in Medline, Embase and Web of Science. Fourteen publications in 10 populations that examined AMD incident cases were identified. Data on age-sex specific incidence of late AMD, geographic atrophy and neovascular atrophy, as well as year of recruitment, AMD grading method and continent were extracted. The annual incidence of late AMD, geographic atrophy and neovascular AMD by age-sex in American whites aged ≥50 years from a Bayesian meta-analysis of incidence studies was compared with incidence extrapolated from published prevalence estimates.

Incidence rates from the review agreed with those derived from prevalence, but the latter were based on more data, especially at older ages and by AMD subtype. Annual incidence (estimated from prevalence) of late AMD in American whites was 3.5 per 1,000 aged ≥50 years, equivalent to 293,000 new cases in American whites per year. Incidence rates approximately quadrupled per decade in age, while annual geographic atrophy rates were 1.9 per 1,000 aged ≥50 years and neovascular AMD rates were 1.8 per 1,000. Late AMD incidence was 38 percent higher in women vs. men.

Am J Ophthalmol 2015;160:1:85-93.

Rudnicka AR, Kapetanakis VV, Jarrar Z, Wathern AK, Wormald R, et al.

A Meta-Analysis of Anti-VEGF For Diabetic Retinopathy

A review of 22 studies involving 1,397 subjects supports the use of anti-vascular endothelial growth factor agents as adjuncts to pan-retinal photocoagulation and pars plana vitrectomy in patients with complicated proliferative diabetic retinopathy. The use of anti-VEGF agents before PRP results in superior functional and structural outcomes at three to four months. The use of anti-VEGF agents before PPV results in decreased duration of surgery, fewer breaks and less intraoperative bleeding. Although

there is evidence for a decreased incidence of early postop vitreous hemorrhage, the quality of evidence is low. Thus, using anti-VEGF agents is primarily a means of facilitating and potentially minimizing the iatrogenic damage that can result from PRP and PPV procedures.

The authors identified randomized controlled trials using anti-VEGF agents, either as stand-alone therapy or combined with other interventions, in the management of proliferative diabetic retinopathy. The primary outcome measures were change in best-corrected visual acuity and (in the context of vitrectomy) duration of surgery and postop vitreous hemorrhage. Secondary outcomes were change in central retinal thickness and (in context of vitrectomy) intraoperative variables suggestive of complex surgery (retinal breaks, intraoperative bleeding, endodiathermy applications). The quality of evidence for all outcomes was appraised using the GRADE criteria.

Of the 22 studies that met criteria for inclusion, one compared intravitreal ranibizumab with saline; one compared intravitreal pegaptanib to PRP; one compared intravitreal bevacizumab to PRP; three compared combined intravitreal ranibizumab/PRP to PRP; five compared combined intravitreal bevacizumab/PRP to PRP alone; and 11 compared combined intravitreal bevcizumab/PPV to PPV alone. There is high-quality evidence to suggest that, when used in conjunction with PRP, intravitreal ranibizumab is associated with superior visual acuity and central retinal thickness outcomes at three to four months. In the context of PPV, there is moderate-quality evidence to suggest that preoperative intravitreal bevacizumab results in significant reduction in the duration of surgery, fewer retinal breaks, less intraoperative bleeding and fewer endodiathermy applications. Although there is evidence to suggest occurrence of early postop vitreous hemorrhage is reduced, the quality of evidence in support of this finding is low.

Retina 2015;35:1931-1941.

Simunovic M, Maberley D.

Use of Anti-VEGF for Neovascular AMD Eyes with Low Vision

A study from Belfast supports the use of anti-VEGF agents in eyes with neovascular age-related macular degeneration presenting with very low visual acuity, particularly when fibrosis and atrophy are absent, and suggests algorithms to predict the outcome for combinations of visual acuity and lesion characteristics across the full visual acuity range.

The researchers performed a retrospective analysis of electronic patient care records of 420 eyes treated with ranibizumab between March 2010 and June 2013. The extracted data was classified into three categories based on patient best-corrected visual acuity as measured on the Early Treatment Diabetic Retinopathy Study charts: 0 to 35 letters; 36 to 69 letters; and ≥70 letters. Best BCVA achieved in year one, and average BCVA over 36 months, were computed. The neovascular lesion type; area of lesion; the presence or absence of hemorrhage; retinal pigment epithelium tear; and atrophy were systematically graded, as was the extent of fibrosis on a categorical scale. Regression anaylsis was performed with the best BCVA achieved in year one as the outcome variable and initial BCVA, person and lesion characteristics as explanatory variables.

The mean change in BCVA from the initial visit to the best-attained BCVA during year one was highly statistically significant with an improvement of 9.95 letters. The improvement from initial BCVA to average BCVA over 36 months was 4.01 letters. Regression analysis identified atrophy and fibrosis as predictors of best BCVA, with the model having an r^2 of 0.71.

Retina 2015:35:1957-1963.

Toth L, Stevenson M, Chakravarthy U.

Assessing Corneal Sensitivity From Meibomian Gland Testing

A study looking at the association between corneal sensitivity and clinical tests that assess the tear film and meibomian glands found that palpebral conjunctival sensitivity may be more critical when assessing dry-eye disease.

Subjects (n=57) were recruited based on the history of contact lens wear and the extent of meibomian gland dropout. The average subject age was 34.7 years (standard deviation: 15.1); 63.2 percent were female. Clinical examination included assessment of symptoms; redness of the lower eyelid margin; lipid layer thickness; esthesiometry of the inferior cornea and palpebral conjunctiva; noninvasive tear breakup time; Schirmer test assessment; and meibomian gland assessment through orifice count and expressed meibum quality grade. The subjects were grouped into a high corneal sensitivity (HS) group or low corneal sensitivity (LS) group, based on the median sensitivity measure. Groups for palpebral conjunctival sensitivity were created in the same manner. Mann-Whitney U tests were used for comparisons of sensitivity groups, and a Spearman rho correlation coefficient was used to study the associations between each tear film characteristic and the sensitivities.

The median corneal and conjunctival thresholds for sensation were 0.5 and 1.4 g/mm^2. The average noninvasive tear breakup time (HS group: 7.8 seconds, interquartile range (IQR) = 5.7; LS group: 11.6 seconds, IQR = 8.4; p=0.05) and Schirmer test assessments (HS group: 16.0 mm, IQR = 15.0; LS group: 25.0 mm, IQR = 19.0; p=0.04) were significantly different between the palpebral conjunctival HS and LS groups. All other group comparisons and correlations were not statistically significant.

Cornea 2015;34:1187-1192.

Left your *Review of Ophthalmology* magazine at the office? No problem!

Read *Review* on the go from any mobile device!

Just simply go to www.reviewofophthalmology.com and click on the digimag link to get your current issue.

FDA Clearance Expands Imaging for Newborns

Visunex Medical Systems announced the Food and Drug Administration's clearance of the PanoCam LT widefield imaging system for the imaging of all newborn infants.

PanoCam LT is a compact, wireless imaging system that is designed to detect a number of external, anterior and posterior segment vision disorders that may have long-term effects on the vision of millions of children worldwide each year. Clinical data suggests that vision disorders may affect between 10 and 20 percent of all newborns globally.

"We are launching the Panocam LT, the first completely wireless, hardware and software solution, to help ophthalmologists and maternal clinicians identify vision disorders in newborns. Our PanoCam LT and the PanoCam Review Software will help clinicians identify newborn vision disorders," that, if treated earlier, may preserve healthy vision, says Visunex CEO, Dr. Wei Su.

An estimated 4 million children in the United States and 130 million globally are born each year. Vision screening is not currently provided as standard of care in most neonatal centers. Research conducted in Asia, Brazil and the United States suggests that one in 70 newborns may have some form of vision disorder.

Most commonly, the first eye test performed on a child is prior to kindergarten at the age of 5 or 6. While many visual disorders may be transient, a growing number of clinicians believe that the screening of newborns may provide early detection of vision disorders, such as retinal hemorrhages, which may be a precursor to amblyopia. Early detection of retinal hemorrhages as well as many other serious disorders can lead to early therapeutic intervention and potentially prevent vision loss. For more information, visit visunexusa.com.

Ziemer Femto Laser Approved

The FDA also granted 510(k) approval for use of the Ziemer Femto LDV Z8 in the United States.

Ziemer says the Femto LDV Z8 offers the first truly mobile femtosecond laser solution for refractive, cornea and cataract procedures to be performed on an all-in-one-system. The laser uses unique technology that provides precision in the cornea and power in the lens with use of adjustable pulse energy combined with a high repetition rate to provide a precise capsulotomy and lens fragmentation, the company reports. The innovative, compact design provides a mobile and versatile workstation made for seamless integration into any physician office or operating room in the country. The Femto LDV Z8 is approved for Z-Lasik and Z-Lasik Z; intracorneal rings; intrastromal pockets; lamellar keratoplasty; penetrating keratoplasty; anterior capsulotomy; lens fragmentation; and clear corneal and arc incisions. For information, visit femtoldv.com or ziemerusa.com.

Multi-Dose Restasis Sought

Allergan has submitted a Prior Approval Supplement (PAS) for Restasis (cyclosporine ophthalmic emulsion) 0.05%, seeking approval of a multi-dose, preservative-free presentation. If approved, the presentation would offer patients the same formula in a multi-dose system with patented uni-directional valve and air filter technology.

Approved by the FDA in 2002, Restasis is the only eye drop that helps increase the eyes' natural ability to produce tears, which may be reduced by inflammation due to chronic dry-eye disease. Restasis did not increase tear production in patients using anti-inflammatory eye drops or tear duct plugs. REVIEW

This article has no commercial sponsorship.

A middle-aged woman with a history of rheumatoid arthritis awakens and discovers visual field loss in one eye.

Ayan Chatterjee, MD, MSEd, and Alex V. Levin, MD, MHSc, FRCSC

Presentation

A 6-month-old boy of Indian descent was referred from an outside hospital for further evaluation of suspected bilateral aniridia. The patient was initially noted to have an abnormal iris by the pediatrician and referred to a pediatric ophthalmologist, who made a diagnosis of aniridia. The child was referred to a geneticist for appropriate molecular genetic testing. Based on the ophthalmologist's diagnosis, sequencing of the PAX6 gene was conducted and found to be normal. Concurrent targeted exon-level oligoarray comparative genomic hybridization (ExonArrayDx, Gene Dx, Gaithersburg, Md.) did not reveal a deletion or duplication involving the PAX6, DCDC1, ELP4 or WT1 genes. Approximately 80 percent of cases of aniridia can be explained by mutations in PAX6.[1] The absence of a deletion in the 11p13 region eliminates the possibility of WAGR (Wilms tumor, Aniridia, Genital malformations, Retardation) syndrome. Therefore, the child was referred to us to clarify the diagnosis.

Medical History

The boy was the product of a single gestation born at 40 weeks, by normal vaginal delivery. He met all appropriate milestones and was noted to be developmentally normal, making eye contact, smiling, laughing, tracking, rolling and sitting up without support. He was on no chronic medications. The maternal side of the family is North Indian, and the paternal side of the family is South Indian. Per report, the maternal grandmother carried a diagnosis of coloboma since childhood.

Examination

The boy's vital signs, height and weight were within normal limits. Systemic physical exam was remarkable for a healthy young boy of Indian descent with no significant external pathology and normal external genitalia.

Ophthalmologic examination revealed normal visual responses for age. Intraocular pressures were 8 mmHg OU by Icare tonometry. Pupils were fixed, round and dilated to 8 mm, with a normal margin demonstrating a physiologic rim of posterior pigmented iris epithelium. The iris was symmetric for 360 degrees in each eye and between eyes *(See Figure 1)*. There was no change in pupil size after instillation of phenylephrine 2.5% and cyclopentolate 1%. Eye movements were full and there was no strabismus or nystagmus. Adnexa, lids and lashes were normal. The conjunctivae were white and quiet. The corneas were clear with no limbal pannus. Slit-lamp examination revealed tiny persistent pupillary membrane strands arising from a poorly developed collarette. Anterior chambers were deep and quiet, and lenses were central and clear with mild residual anterior peripheral tunica vasculosa lentis. Fundus examination was entirely normal OU with well-developed fovea, macula and optic nerves. Cycloplegic refraction was OD +8.00 sphere and OS +7.50 sphere.

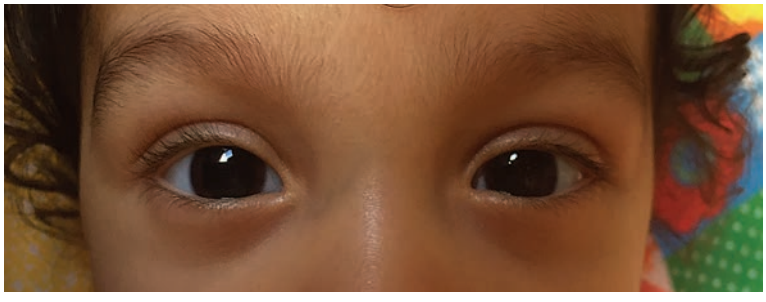


Figure 1. Photograph of the eyes is notable for small, 1 to 2 mm iris remnants spanning 360 degrees with large pupils in the undilated state OU, unchanged post-dilation.

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

Diagnosis, Workup and Treatment

The presence of symmetric and otherwise normal, fixed dilated pupils in a child with an otherwise normal eye examination is most consistent with a diagnosis of congenital hypoplasia of the iris sphincter/dilator. Given the boy's high hyperopia and the possibility of impaired accommodation in this disorder, glasses were prescribed. Furthermore, we recommended echocardiogram to rule out structural abnormalities that have been associated with this diagnosis.

Discussion

Recognizing aniridia in infants is important given the high risk for cataracts (73 percent), glaucoma (46 percent) and keratopathy (45 percent) in addition to the possible association with WAGR syndrome, and thus potentially life-threatening Wilms tumor.[2] Aniridia may occur sporadically or with a positive familial history. The estimated overall prevalence is between 1:64,000 and 1:96,000.[3] It is a panocular disorder characterized by variable expression which usually includes nystagmus and macular hypoplasia. Other features such as corneal pannus; cataract (in particular anterior pyramidal); glaucoma; refractive error; strabismus; and rarely, retinal degeneration may be present in patients. The iris may show a wide variety of appearances, ranging from almost complete absence to varying degrees of residual iris, usually asymmetric in a given eye and between eyes. The pupils may or may not be responsive to mydriatics, largely depending on the amount of residual iris. Persistent pupillary membrane strands may be seen, but usually only if the collarette is preserved. Aniridia may occur due to mutations or small deletions within the PAX6 gene, or as part of a larger deletion involving chromosome 11p13 that may include the WT1 gene, resulting in WAGR syndrome. Until WAGR system has been ruled out by molecular testing, renal ultrasound screening is indicated. Infants with WAGR syndrome require ongoing screening until at least 7 to 8 years old.

The differential diagnosis of fixed dilated pupils includes other disorders. Gillespie syndrome is an extremely rare autosomal recessive syndrome that is associated with symmetric, fixed, dilated pupils with scalloped pupillary margins, persistent pupillary membrane strands, cerebellar ataxia and developmental delay.[4] Instillation of mydriatic compounds, perhaps inadvertently through contact with plants (e.g., members of the genus brugmansia, such as the angel's trumpet[5,6] or ingestion of atropa belladonna berries, which can be mistaken for blueberries[7]) or non-ocular compounds (e.g., inadvertent contamination of the eye after handling scopolamine patches[8-10] or antiperspirant powders containing diphemanil methylsulfate[11]), will result in fixed dilated but otherwise normal morphology pupils. Traumatic mydriasis is usually unilateral and asymmetric with an irregular pupil due to visible iris sphincter tears. Systemic disorders with bilateral mydriasis present with signs and symptoms that are usually readily apparent, for example, congenital hypoventilation syndrome (Ondine's curse).

Recognition of congenital hypoplasia of the pupillary sphincter/dilator allows for appropriate intervention and allows elimination of concerns for ocular and renal prognosis associated with aniridia.

Congenital absence of the pupil sphincter and dilator muscle (sometimes called congenital mydriasis) is exceedingly rare, affecting far more females than males.[12-17] Fewer than 20 cases have been reported in the English literature. The appearance is distinctly different from aniridia in that the iris is symmetrically enlarged beyond 6 mm and symmetric between the two eyes with an otherwise normal morphology and normal pupil margin, although the collarette may appear somewhat underdeveloped. Most importantly, the remainder of the eye examination is normal. Accommodation may be impaired.[18] Rare systemic associations include patent ductus arteriosus (PDA)[14,15] and thus echocardiography may be indicated. Congenital mydriasis may also occur as part of the multisystem smooth muscle dysfunction syndrome (MIM 613834) caused by mutations in the ACTA2 gene. These patients have PDA, thoracic aneurysms and other vasculopathy, and may have other evidence of smooth muscle dysfunction including hypoperistalsis. The iris malformation is

(continued from page 35)

benefit from outside help, there are a number of consulting firms out there that will do all of this for you."

The Doctor Still Counts

"Today's exams are definitely more technology-driven," notes Dr. Awdeh. "A patient coming in for an exam may receive a battery of tests and imaging before seeing the ophthalmologist, so we already have a good idea of what's going on with the patient by the time we see him. In the future we may not only be able to look at the tests done during that visit and previous visits, but also have information from home monitoring of relevant metrics. We'll have an extensive dataset to analyze that should help give us a solid diagnosis and help us create a plan for moving forward. Whether that will make our job easier is another question, because we'll have even more data points and pieces of information to assimilate in a short amount of time. It might make our jobs harder. It will definitely make the analytical and problem-solving abilities of the doctor even more critical during the examination.

"However, the history and physical examination will continue to be an important part of medicine," he adds. "I don't see that being replaced by technology, at least in the next 10 years. I think technology will simply supplement our role as physicians, and the role of patients in the examination."

"In the future I think patients will see doctors employ clinical decision support tools from an artificial intelligence source such as IBM Watson," says Dr. Chang. "Supercomputer neural networks and deep learning are being applied to digitized health information. Nevertheless, people don't want a robot taking care of them; they want a human with empathy. In my mind, that's probably the most important thing the physician provides, along with good outcomes. Everyone wants the highest-quality care delivered by a person who understands his perspective and cares about him."

"Patients still want to talk to the doctor," agrees Dr. Lord. "They still want to meet face to face and have the doctor be upfront and transparent about what their situation is. We've gotten better at using tools like instructional videos, helping patients understand what their condition is and what their surgical needs are, and we have better instruments, but I'm pretty sure the doctor-patient interaction hasn't changed much.

"On the other hand, we're being pushed to be more accessible and digital in many areas," he says. "We're managing electronic records; the vast majority of our prescriptions have to be sent electronically. Our EHR systems are being designed so that we can digitally communicate, doctor to doctor. We're expected to communicate with our patients electronically. Of course, there are good and bad sides to this. It's a monster project to get all of this up and running. But in the right practice, all the digital communication does reduce the number of phone calls and helps with medico-legal issues. And either way, for good or bad, it's the way things are headed."

Dr. Lord believes the trend toward digital, mobile interaction is likely to continue for some time to come. "The baby-boomer generation is now one of our prime demographics, and I don't know many baby boomers that haven't adopted this kind of technology," he says. "My parents are in that demographic, and they're pretty tech-savvy—and they're from a small town. I think that if your practice hasn't adjusted to this, it needs to. This is not going away." REVIEW

Dr. Chang has a financial interest in the EyeGo intellectual property. Dr. Awdeh has a financial interest in the CheckedUp platform. Dr. Lord is a partner in Cloud Nine Development, developer of the Eye Handbook app; however, Dr. Lord notes that the app is free online.

---

often associated with iris flocculi (large cysts at the pupil margin).

In conclusion, recognition of congenital hypoplasia of the pupillary sphincter/dilator allows for appropriate intervention and allows elimination of concerns for ocular and renal prognosis associated with aniridia. Echocardiography may be utilized to rule out cardiac malformations. REVIEW

1. Gronskov K, et al. Population-based risk estimates of Wilms tumor in sporadic aniridia. A comprehensive mutation screening procedure of PAX6 identifies 80% of mutations in aniridia. Hum Genet 2001;109:11-18.
2. Netland P, Scott M, Boyle J, Lauderdale J. Ocular and systemic findings in a survey of aniridia subjects. J AAPOS 2011;15:562-566, doi:10.1016/j.jaapos.2011.07.009.
3. Nelson L, Spaeth G, Nowinski T, Margo C, Jackson L. Aniridia. A review. Surv Ophthalmol 1984;28:621-642.
4. Nelson J. Flaherty M, Grattan-Smith P. Gillespie syndrome: a report of two further cases. Am J Med Genet 1997;71:134-138.
5. Vunda, A. & Alcoba, G. Images in clinical medicine. Mydriasis in the garden. N Engl J Med 2012;367:1341, doi:10.1056/NEJMicm1208053.
6. Plummer C, Dangoor A. The trumpet's blown pupil. Med J Aust 2015;202:497.
7. Mateo Montoya A, Mavrakanas N, Schutz J. Acute anticholinergic syndrome from Atropa belladonna mistaken for blueberries. Eur J Ophthalmol 2009;19:170-172.
8. Rosen N. Accidental mydriasis from scopolamine patches. J Am Optom Assoc 1986;57:541-542.
9. Rubin M, Sadoff R, Cozzi G. M. Unilateral mydriasis caused by transdermal scopolamine. Oral Surg Oral Med Oral Pathol 1990;70:569-570.
10. Ng J, Li Yim J. Accidental Unilateral Mydriasis from Hyoscine Patch in a Care Provider. Semin Ophthalmol 2015 Aug 21:1-2.
11. Silbert P, Edis R. Accidental mydriasis due to prantal powder. Aust N Z J Med 1991;21:929.
12. White B, Fulton M. A rare pupillary defect: Inherited by Identical Twins. J Hered 1937;28:177-180.
13. Richardson P, Schulenburg W. Bilateral congenital mydriasis. Br J Ophthalmol 1992;76:632-633.
14. Graf M, Jungherr A. Clinicopathologic reports, case reports, and small case series: Congenital mydriasis, failure of accommodation, and patent ductus arteriosus. Arch Ophthalmol 2002;120:509-510.
15. Lindberg K, Brunvand L. Congenital mydriasis combined with aneurysmal dilatation of a persistent ductus arteriosus Botalli: A rare syndrome. Acta Ophthalmol Scand 2005;83:508-509, doi:10.1111/j.1600-0420.2005.00496.x (2005).
16. Rao, A. Isolated bilateral congenital iris sphincter agenesis. Case Rep Ophthalmol Med 2011;479092, doi:10.1155/2011/479092.
17. Caccamise W, Townes P. Bilateral congenital mydriasis. Am J Ophthalmol 1976;81:515-517.
18. Buys Y, Buncic J, Enzenauer R, Mednick E, O'Keefe M. Congenital aplasia of the iris sphincter and dilator muscles. Can J Ophthalmol 1993;28:72-75.

Equipment and Supplies

Equipment and Supplies

Practice For Sale

Career Opportunities

General Ophthalmologist

Minneapolis/St. Paul, Minnesota

HealthPartners Medical Group is a successful multi-specialty physician group based in Minneapolis/St. Paul, central Minnesota and western Wisconsin. Our busy Eye Care Division includes Ophthalmology, Optometry, and full service Optical. Our group of 14 Ophthalmologists includes general ophthalmologists as well as subspecialists in oculoplastics, pediatrics and retina. We're part of a highly regarded ACO, providing quality eye care to a large portion of the Twin Cities at our six well-equipped, state-of-the-art HealthPartners Eye Clinics.

We seek a full-time, BC/BE general Ophthalmologist for our metro-area practice, and encourage those with fellowship-training to apply. In addition to clinical and surgical responsibilities, you'll share in reasonable call coverage at Regions Hospital, our nationally recognized Level 1 trauma center in St. Paul.

We offer a great team of colleagues, generous benefits and compensation, and the excitement of a metropolitan practice and lifestyle. Apply online at **healthpartners.com/careers** or email your CV and cover letter to **sandy.j.lachman@healthpartners.com**. EOE

HealthPartners®

healthpartners.com

UF UNIVERSITY of FLORIDA
College of Medicine

FULL-TIME FACULTY
VITREORETINAL SURGERY, OCULOPLASTICS AND CORNEA/EXTERNAL DISEASES

The Department of Ophthalmology at the University of Florida has current full-time faculty employment opportunities in the areas of Vitreoretinal Surgery, Oculoplastics and Cornea/External Diseases. Salary and rank will be commensurate with credentials and experience. The College of Medicine has an active compensation plan which includes incentives and bonuses. Employer will assist with relocation costs.

Our new Chair, Dr. Sonal Tuli and her entire team are extremely excited as we begin our journey to becoming the premier eye department in the country with exceptional clinical care and cutting-edge research.

Candidates should apply through the Careers at UF website https://jobs.ufl.edu/ and upload the following required documents:

- Letter of Application Stating Goals
- Curriculum Vitae
- Letters of Reference (minimum of 3)

Gainesville is a charming city and home to the University of Florida. The area is known for its natural beauty, with many springs, lakes and rivers. The mild climate allows for many outdoor activities and residents enjoy swimming, boating, fishing, bicycling and camping. Culturally, the city is enriched by the influence of the university. The population of Gainesville is approximately 111,000 with a surrounding population of 250,000. We have a diverse culture, excellent public schools, low cost of living and no state income tax. For the past 8 years Gainesville has been voted among the Top 12 Most Livable Cities in the Nation by Money Magazine.

Any questions regarding this position should be directed to Christina Kuruppacherry with the Department of Ophthalmology at (352) 273-8776 or kuruppcl@ufl.edu.

The University of Florida is an Equal Opportunity Institution dedicated to building a broadly diverse and inclusive faculty and staff. The selection process will be conducted in accord with the provisions of Florida's 'Government in the Sunshine' and Public Records Laws.

IMMEDIATE OPENINGS
Hagerstown, MD/Chambersburg, PA

High volume cataract and glaucoma practice seeks cataract/cornea/anterior segment/glaucoma ophthalmologists. State of the art clinical equipment and on site ASC. We desire motivated, patient-focused candidates with excellent surgical skills who seek to practice in a team practice setting. Maryland and PA license preferred. Salary with productivity bonus and partnership opportunity in both practice and ASC.

Send CV to: Kris Culler
Fax 717-262-9714
Email: kculler@ludwickeyecenter.com

Ludwick Eye Center
825 Fifth Ave
Chambersburg, PA 17201

REVIEW Advertising Index

For advertising opportunities contact:

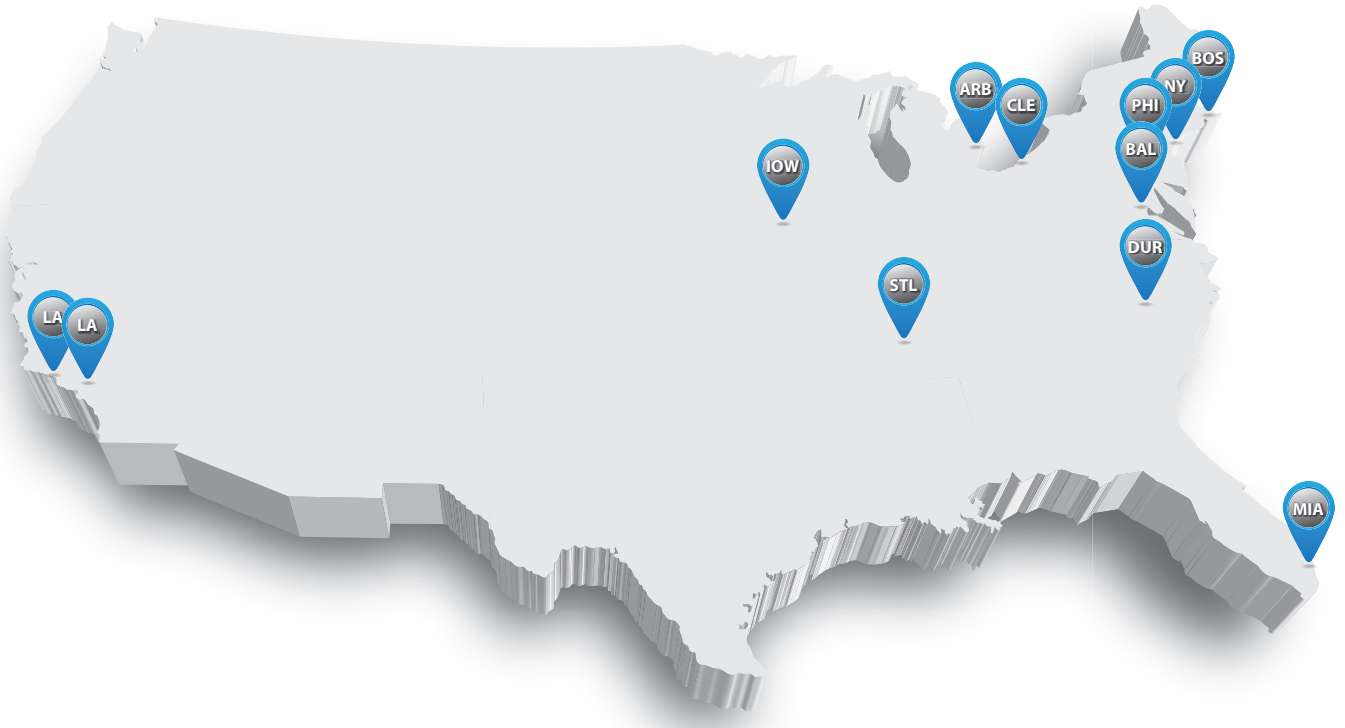
Michelle Barrett (610) 492-1014
or mbarrett@jobson.com

James Henne (610) 492-1017
or jhenne@jobson.com

Michael Hoster (610) 492-1028
or mhoster@jobson.com

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

Great Company



Where will you find Keeler's Vantage Plus? Easy...the top 12 ophthalmology centers in the US*.

Keeler Vantage Plus

- Intelligent Optics for superior views (US Patent: 8,132,915)
- HiMag™ Lens for detailed magnified views
- Convertible Illumination LED and Xenon
- Lightest Wireless System

Get a
Free Keeler Indirect
When You
Buy Any 3 Keeler Indirects,
& Trade-in Any 3 Indirects
through December 31, 2015

Learn more at www.keelerusa.com

Buy Online!
keelerusa.com

Keeler
OPTICS

*Top-ranked hospitals for ophthalmology – Source: U.S. News & World Report

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

Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

THE DRY EYE TREATMENT SHE NEEDS TODAY. BECAUSE TOMORROW MATTERS.

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

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

Indication and Usage

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

Important Safety Information

Contraindications

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

Warnings and Precautions

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

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® ophthalmic emulsion.

Adverse Reactions

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

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

Reference: 1. RESTASIS® Prescribing Information.

ALLERGAN