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SPECIAL REPORT
ARVO 2013
HIGHLIGHTS

In This Issue

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ARVO Meeting Highlights

POSTMORTEM PUPILLARY DILATION POSSIBLE

SEATTLE :: **PUPILS CAN BE PHARMACOLOGICALLY DILATED** after death, according to the results of a recent study.

The study examined pupillary dilation of postmortem eye bank eyes, which may facilitate postmortem examination and screening through modalities such as fundus photography and fundus optical coherence tomography (OCT).

"Pupillary dilation of postmortem eyes should lead to easier and more effective postmortem fundus photography and OCT," said Jeffrey R. Golen,

(See story on page 9)

New glaucoma drug significantly lowers IOP

Beta blocker-free, fixed-dose therapy combines brinzolamide 1%, brimonidine tartrate 0.2% into one multidose bottle

24% to 35% Mean IOP Reduction at Month 3

	FIXED-COMBINATION (SIMBRINZA) (%)†	BRINZOLAMIDE (%)	BRIMONIDINE (%)
8 AM	– 26.6%	– 22.6%	– 17.1%
10 AM	– 34.9%	– 22.4%	– 25.8%
3 PM	– 24.1%	– 16.9%	– 14.3%
5 PM	– 29.7%	– 17.7%	– 23.9%

†$p \leq 0.002$ versus brinzolamide or brimonidine across all time points

By Lynda Charters;
Reviewed by Gregory J. Katz, MD

BASEL, SWITZERLAND :: **A NEW FIXED-DOSE** combination medication for the reduction of elevated IOP may provide patients with primary open-angle glaucoma or ocular hypertension with the best of two worlds.

The recent FDA approval of the fixed-dose combination medication (Simbrinza, Alcon Laboratories) combines brinzolamide 1%, a carbonic anhydrase inhibitor, and brimonidine tartrate 0.2%, an alpha 2 adrenergic receptor agonist, in one multidose bottle. The efficacy of the combination is superior to the effects of the two components administered separately.

In addition, it is the only available, fixed-dose combination therapy for glaucoma in the United States without a beta blocker, according to the manufacturer.

'Nearly 40% of patients required two or more medications after 5 years in the Ocular Hypertension Treatment Study.'
– Gregory J. Katz, MD

Gregory J. Katz, MD, a glaucoma specialist at St. Joseph Mercy Medical Center, Ann Arbor, MI, commented on the convenience that the combined dosing provides.

"Many patients with glaucoma end up needing more than one medication," Dr. Katz said. "For example, nearly 40% of patients required two or more medications after 5 years in the Ocular Hyper-

*(Continues on page 8 : **Fixed-dose therapy**)*

If only you could predict how ocular inflammation will behave.

DUREZOL® Emulsion now has head-to-head data vs prednisolone acetate in patients with endogenous anterior uveitis.[1]

Scan the QR code with your smartphone or log on to **www.inflammationhappens.com** to see the results for yourself.

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

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

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

Warnings and Precautions

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

Adverse Reactions

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

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

Reference: 1. DUREZOL® Emulsion Package Insert.

Alcon®

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

InDispensable

General

Special Report

ARVO MEETING HIGHLIGHTS

In Every Issue

The lesson of Flight 214

Having a disaster in the OR is analogous to a problem in the cockpit

By Peter J. McDonnell, MD

director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of *Ophthalmology Times*.

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PETER PRONOVOST, MD, PHD, is an anesthesiologist at my hospital. He is also a specialist on patient safety, quality of medical care, and reducing medical errors. It was while he was a college student and his father's cancer was misdiagnosed that he became interested in this area of safety and quality. By the time a second opinion provided the correct diagnosis, it was too late to give the appropriate therapy, and his father died "a horrible death, writhing in pain." In 2008, Dr. Pronovost was awarded a MacArthur Fellowship—the so-called "genius grant."

Even physicians are humans, and therefore prone to imperfection and the occasional mistake. But Dr. Pronovost believes it is possible to put in place protocols and strategies to reduce (or, in some cases, eliminate) mistakes and harm to patients.

AN OUNCE OF PREVENTION

About a year ago, we were discussing the causes of serious problems (like death) that occur in the OR. Dr. Pronovost told me that having a disaster in the OR is analogous to having a problem in a cockpit that leads to a plane crash. When you hear that a crash was the result of "pilot error," almost always the subsequent investigation shows the same thing—the pilots did not know each other and had never flown together before. Each one had different presumptions about who knew what and who was doing what. Almost always, prompt communication in the cockpit could have prevented the crash.

Because the data were so compelling with regard to plane crashes, Dr. Pronovost thought it made no sense at all for surgeons, anesthesiologists, and nurses who did not know each other to be involved in complex surgeries. If everyone knew and was comfortable communicating with each other, then at the first hint of trouble the issue could be addressed promptly and a delay in management avoided. If people don't communicate (say the nurse is intimidated by a surgeon he or she has not met before, or the surgeon incorrectly presumes the anesthesiologist is doing something the usual anesthesiologist does) then problems may not be articulated or fixed quickly.

That discussion came to mind when I learned about Asiana Flight 214 crash landing at the SFO airport. Sadly, three deaths occurred and many passengers were seriously injured. A television news report described how the plane struck short of the runway, its tail section was knocked off, and a fire promptly threatened the passengers. According to the report, the plane was flying too low and at too slow a speed.

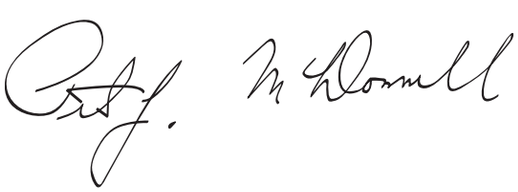
"I bet the people in the cockpit had never flown together before," I said to the person next to me, as we listened to the newscast. Before long, the reporter shared the information that, in fact, there had been three pilots in the cockpit on that transoceanic flight and none of the three had ever flown together.

"That's amazing that you knew that," said my companion.

"Yes, it is," I replied.

A MATTER OF TEAMWORK

The lesson of Flight 214 for us in medicine is that we should be creating teams of people (physicians, nurses, anesthesiologists, technicians, etc.) who know each other, can anticipate what is next, and communicate well. We should not put people together in ORs or intensive-care units who are strangers or not "team players." High-volume ophthalmic surgeons already know this, as they invariably have "favorite" scrub nurses and anesthesiologists. To do otherwise is to put patients at unnecessary risk. ■



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- *http://www.european-hospital.com/en/article/9591-Patient_safety_expert_Peter_Pronovost_earns_dual_national_honors.html*
- *http://www.timesheraldonline.com/news/ci_23631983/details-emerge-about-flight-214s-cockpit-chaos*

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In partnership with our readers, we will achieve mutual success by:

- Being a forum for ophthalmologists to communicate their clinical knowledge, insights, and discoveries.
- Providing management information that allows ophthalmologists to improve and expand their practices.
- Addressing political and socioeconomic issues that may either assist or hinder the ophthalmic community, and reporting those issues and their potential outcomes to our readers.

REPORT:
Eye disorders cost $139 billion per year

Communication, advocacy by ophthalmologists among solutions

By Ron Rajecki

Direct and indirect costs associated with eye disorders and vision loss total $139 billion per year, according to a research commissioned by Prevent Blindness America (PBA).

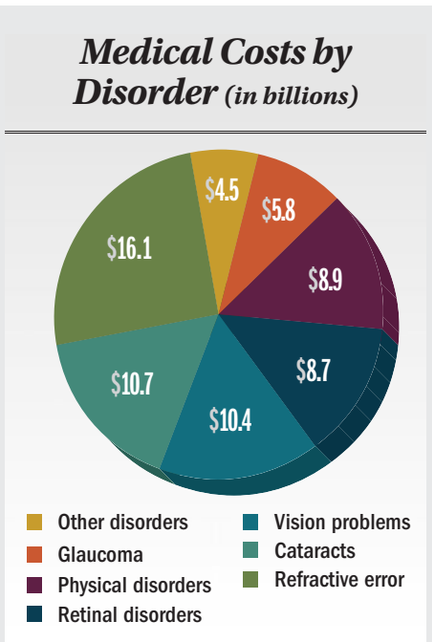
The amount, noted in the "Cost of Vision Problems" report, puts eye disorders ahead of hypertension, diabetes, and stroke when it comes to direct costs. Heart disease, cancer, emotional disorders, and pulmonary conditions are the only major chronic diseases in the United States that have higher direct costs.

"I don't think eye health gets the attention nationally in our public health sector that these other chronic conditions get, largely because those conditions often result in death if nothing is done with them," said Jeff Todd, JD, MS, chief operating officer of PBA. "But the cost of eye disorders to our society is right up there with these other conditions, and so we need to pay attention to that."


Todd

Direct costs, accounting for 48% of the $139 billion total, include expenses associated with diagnosed disorders and undiagnosed, self-reported vision loss; medical vision aids and vision-assistive devices and adaptations; and services, such as special education, school screening, and assistance programs. Indirect costs include productivity losses, nursing home and informal care, and entitlements and tax deductions.

Annually, patients and their families are paying 52% of the total, primarily for costs associated with productivity losses and informal care. The federal government and private insurers are footing the bill for 32% and 16% of the total, respectively, mostly for direct medical costs and long-term care. (The federal government also pays for entitlement programs and tax deductions attributable to blindness but not included in the report's total costs.)



(FIGURE 1) Refractive error is the most expensive eye condition at $16.1 billion per year. Cataracts are the second costliest.

WHAT OPHTHALMOLOGISTS CAN START DOING NOW

Ophthalmologists can take several actions to help lower costs associated with vision-related diseases, said Todd as well as John Wittenborn, one of the University of Chicago researchers who conducted research on behalf of PBA.

- **Improve communication and coordination of care with other eye-care professionals (ECPs) and primary-care providers (PCPs).**

"We need to encourage increased collaboration across all health-care fields, because people are going to need to have a more comprehensive approach to their health care," Todd said.

Continues on page 7 : **Cost of vision**

HEADLINES YOU MIGHT HAVE MISSED

AS SEEN IN *Ophthalmology Times*' weekly eReport. Sign up at *http://www.modernmedicine.com/OphthalmologyTimes/enewssignup*

SUBRETINAL IMPLANT EARNS CE MARK

RETINA IMPLANT AG, developer of subretinal implants for patients blinded by retinitis pigmentosa, has received the CE Mark for its wireless subretinal implant technology (Alpha IMS). ***http://bit.ly/1boVyly***

ELLEX SLT THERAPY LAUNCHES IN U.S.

ELLEX MEDICAL LASERS LTD. announced the launch of its proprietary selective laser trabeculoplasty (SLT) technology in the United States. SLT advanced laser therapy, which is non-invasive and non-thermal, stimulates a natural healing response in the eye to treat glaucoma. ***http://bit.ly/1boU5fb***

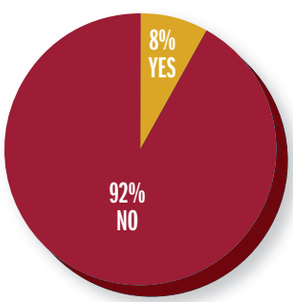
EYE DISEASE PATIENT DATABASE COMING

THE AMERICAN ACADEMY OF OPHTHALMOLOGY (AAO) plans to implement the first comprehensive eye disease patient database in the United States. The Intelligent Research in Sight Registry is a centralized data repository and reporting tool that collects data from electronic health records and performs statistical analysis of aggregated, de-identified patient data to produce easy-to-interpret, national and practice-level benchmark reports. ***http://bit.ly/12HabvP***

Facebook Poll

WE ASKED: Is there a shortage of ophthalmologists in your community now?

YOU SAID:



COST OF VISION

(Continued from page 6)

Coordinating care not only could help detect and treat vision problems earlier, lowering costs; it also could assist with patient adherence to therapy recommendations, especially with patients with diabetes, he added.

"Diabetics face many different health conditions that they are having to juggle, and they often are seeing multiple providers. It's easy for them to lose track of medications or appointments and to lose track of their health altogether," Todd said. "So the more we can work together as a health-care system to make it easier for patients to address their health-care needs, the better."

Telemedicine and other advances, such as electronic health records, should ease information-sharing and care coordination between ECPs and PCPs. For instance, PCPs could perform retinal imaging that ophthalmologists could read remotely and then provide guidance, increasing services available to patients.

"We also have some work to do educating PCPs about paying attention to the eye and encouraging their patients to seek follow-up care when needed, and to address those concerns that they can within their own offices," Todd said.

The sharing of care, as appropriate, among ophthalmologists, optometrists, and PCPs will help ensure that health-care professionals can keep up with the demand for eye-care services, he added.

> Educate patients that neglecting vision care now could lead to more costly expenses later.

"The costs of vision problems . . . add up, and it's worth letting the patients know," Todd said. "It's not only about their health; losing your sight is costly."

"Patients must understand that they will end up paying for the bulk of costs from eye disorders and low vision," Wittenborn said. "Loss of vision is not only a quality-of-life issue; it is a very substantial financial issue for patients, their families, and the nation. This puts the value of proper eye care and prevention in stark relief."

> Advocate for increased or maintained funding for prevention of vision-related problems.

The Centers for Disease Control and Prevention's Vision Health Initiative (VHI) receives annual funding of $481,000, or $0.00000346 for every dollar that vision problems cost American society every year, Todd said.

"Only a few years ago, the VHI was at $3 million annually," he noted. "Without a sufficiently funded, dedicated federal program to address vision problems, the prevalence and costs of these problems will only increase."

Todd said that PBA is "encouraging everyone to advocate for increased funding or at least a maintained level of funding" for prevention efforts.

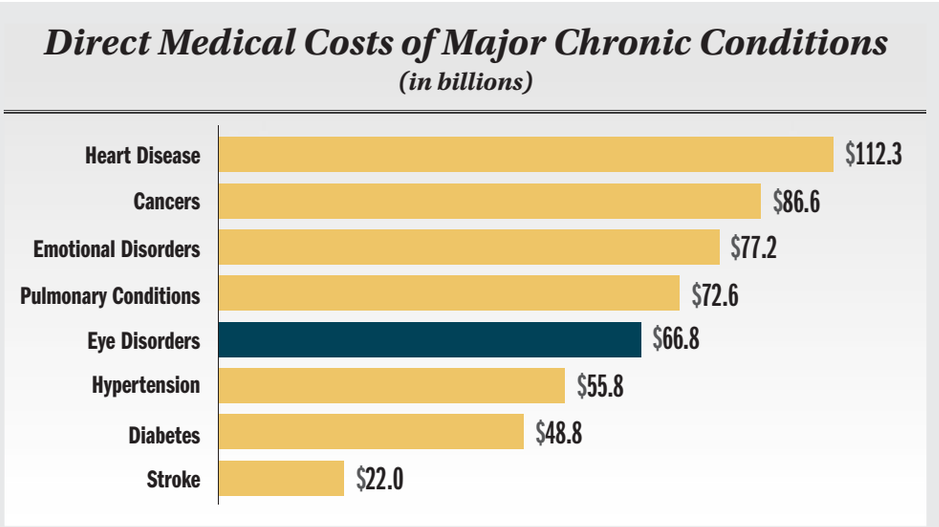
Preventive care will decrease costs, Wittenborn said. The report indicates that eye disorder and vision loss costs disproportionately affect the oldest Americans, he said, and because this group is set to be the fastest-growing segment of the population, these costs are expected to continue to grow.

"If there is any good new in this, it is that most of the costs to society are indirect costs—consequences of low vision, such as productivity losses, informal care, and long-term care placement," Wittenborn added. "These are costs that can be avoided by preventing vision loss."

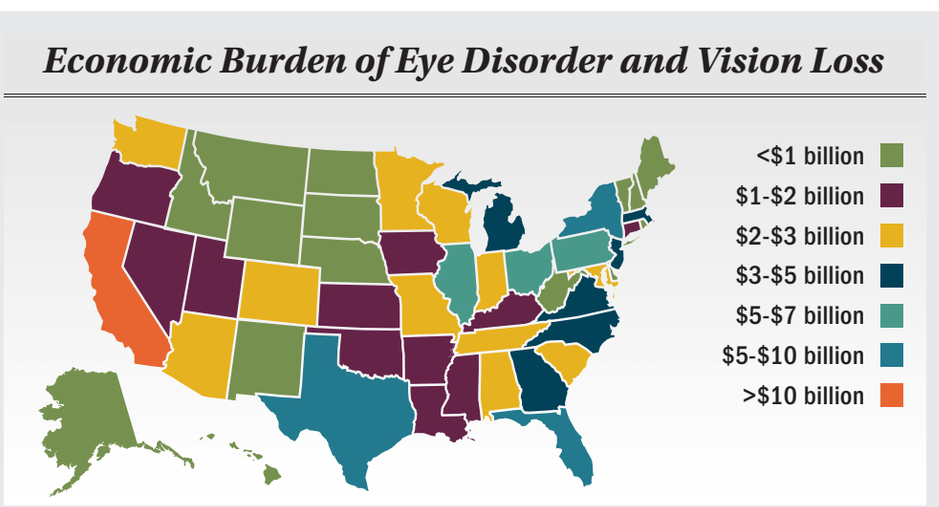
Recent advances, such as molecular therapies for age-related macular degeneration, while seemingly costly in and of themselves, have the potential to avoid even greater costs by preventing or delaying vision loss, he added.

The new research updates a 2007 PBA report, uses revised methodology and cost data across the age spectrum (including children for the first time), and considers all disorders related to the eye.

The full report can be accessed at *http://costofvision.preventblindness.org.* ■



(FIGURE 2) **Heart disease, cancer, emotional disorders, and pulmonary conditions are the only major chronic diseases in the United States that have higher direct costs than eye disorders.**



(FIGURE 3) **The report estimated state-specific burden by allocating the costs to each state on the basis of their population for each age group. The analysis does not include any differences in state-specific unit cost estimates, so state values are solely a function of the per-person burden estimate by age group and the population of each age group in each state.** *(Figures courtesy of Prevent Blindness America)*

FIXED-DOSE THERAPY

(Continued from page 1)

tension Treatment Study. Fixed combinations combine two active ingredients in one bottle.

"This allows for administration of fewer drops in fewer bottles, less exposure to preservatives, and the elimination of the potential for washout effect, and it results in one co-payment compared with two co-payments for the patient," he added.

In addition, other fixed-combination glaucoma medications that are available contain a beta blocker, which has the potential to exacerbate congestive heart failure, asthma, and emphysema, as well as a variety of other medical conditions, he noted.

One drop of the medication is instilled into the affected eye(s) three times daily.

APPROVAL BASED ON TWO TRIALS

The FDA approval of the product was based on the results of two phase III multicenter studies, one of which was conducted by Dr. Katz and colleagues and included 660 patients with open-angle glaucoma or ocular hypertension. In this study, patients were randomly assigned 1:1:1 to treatment with the combination of brinzolamide 1% and brimonidine 0.2%, brinzolamide 1%, or brimonidine 0.2%. The patients instilled the drugs three times daily for 3 months.


Dr. Katz

The main outcome measure was the mean IOP at the 3-month evaluation at four time points (8 and 10 a.m. and 3 and 5 p.m.).

The investigators, who reported their findings (*JAMA Ophthalmol*. 2013;131:724-730), found that the mean IOP in the combined therapy group ranged from 16.3 to 19.8 mm Hg at the four time points. This range was significantly ($p \leq 0.002$ and $p < 0.001$, respectively) lower compared with the results achieved when brinzolamide (19.3 to 20.9 mm Hg) and brimonidine (17.9 to 22.5 mm Hg) were administered separately.

"At all four time points, the brinzolamide-brimonidine group demonstrated the largest percentage reduction in IOP from baseline to the 3-month visit," the investigators reported. "At 3 months, the brinzolamide-brimonidine group had IOP reductions ranging from 24.1% to 34.9% (across time points), the brinzolamide group IOP reductions ranged from 16.9% to 22.6%, and the brimonidine group reductions ranged from 14.3% to 25.8%."

Thirty-four patients did not complete the study because of adverse effects that were not serious but related to the treatment. The most common of these were blurred vision, eye irritation, dysgeusia, dry mouth, and ocular allergy—all occuring in 6% or less of patients. There were no serious adverse events that were considered to be related to treatment in the combined treatment group. Most adverse effects were ocular in nature, and occurred in 22.9% of the combined-treatment group, 18.6% of the brinzolamide group, and 17.3% of the brimonidine group.

Use of the fixed-combination product has significant IOP-lowering capabilities when compared with either of the two drugs administered separately to treat open-angle glaucoma or ocular hypertension and has a safety profile that is consistent with those of the two components, the investigators concluded.

"Glaucoma must be treated over the patient's life, and elevated eye pressure must be managed every day," Dr. Katz said. "It's exciting now to have a product available that combines two effective compounds in one multidose combination, offering sustained control with an excellent safety profile." ■

Safety Profile, Month 3

MOST COMMON TREATMENT ADVERSE EVENTS*	FIXED-COMBINATION (SIMBRINZA) N (%)	BRINZOLAMIDE N (%)	BRIMONIDINE N (%)
Vision blurred	13 (6.1%)	14 (6.2%)	1 (0.5%)
Ocular hyperemia	7 (3.3%)	2 (0.9%)	9 (4.1%)
Eye irritation	6 (2.8%)	2 (0.9%)	4 (1.8%)
Dry eye	2 (0.9%)	2 (0.9%)	6 (2.7%)
Dysgeusia (bad taste)	8 (3.7%)	14 (6.2%)	0
Dry mouth	7 (3.3%)	0	6 (2.7%)

*Adverse events occurring at >2% in any treatment group; Total enrolled (n = 660)
(Tables courtesy of Gregory J. Katz, MD)

GREGORY J. KATZ, MD
E: *glbjkatz@hotmail.com*
Dr. Katz is on the speaker's bureau and is a consultant for Alcon Laboratories.

B+L femtosecond laser gets Health Canada MDL

VAUGHAN, CANADA, AND MUNICH, GERMANY ::
BAUSCH + LOMB ANNOUNCED that its femtosecond laser platform (Victus) was issued a Health Canada Medical Device Licence (MDL). Capable of supporting cataract and corneal procedures on a single platform, the device offers greater consistency and precision over manual cataract surgery techniques, said the company in a prepared statement.

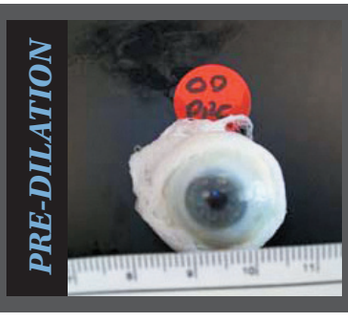
The platform is one of the only femtosecond lasers in Canada with a licence for the creation of a corneal flap in patients undergoing LASIK, anterior capsulotomy during cataract surgery, penetrating arcuate cuts/incisions in the cornea, and laser-assisted lens fragmentation during cataract surgery. Bausch + Lomb Technolas (Technolas Perfect Vision GmbH) has been installing the platforms in surgery centers globally since it received CE mark in November 2011 and FDA clearance in July 2012.

"[This] platform delivers major advancements in cataract and refractive surgery, allowing ophthalmic surgeons to perform multiple bladeless, sight-enhancing procedures on a single system," said Jonathan Abrams, commercial director for Bausch + Lomb Surgical, Canada. "We are committed to playing a leadership role in advancing femtosecond laser technology by working with ophthalmic industry leaders and professional societies alike. We look forward to introducing this technology in Canada." ■

MEANINGFUL PHARMACOLOGIC PUPIL DILATION POSSIBLE AFTER DEATH

How phenomenon may prove useful for postmortem diagnoses for clinicians, forensic examinations

By Lynda Charters; *Reviewed by Jeffrey R. Golen, MD*



(Figure 1a) Pre-dilation photograph of a globe taken 24 hours after time of death (Subject H).

(Figure 1b) 60 minutes post-dilation in the same eye. *(Images courtesy of Jeffrey R. Golen, MD)*

take-home

- **Pupillary dilation of postmortem eyes has been studied to facilitate examinations of ocular diseases after death.**
- **Potential applications of this protocol may even extend to postmortem diagnoses for clinicians and forensic examinations for other purposes.**

SEATTLE ::

Pupils can be pharmacologically dilated after death, according to the results of a recent study.

The study examined pupillary dilation of postmortem eye bank eyes, which may facilitate postmortem examination and screening through modalities such as fundus photography and fundus optical coherence tomography (OCT).

"Pupillary dilation of postmortem eyes should lead to easier and more effective postmortem fundus photography and OCT," said Jeffrey R. Golen, MD, at the annual meeting of the Association for Research and Vision in Ophthalmology. "This may be useful for eye banks for screening specimens for specific research interests."

Potential applications of this protocol may even extend to postmortem diagnoses for clinicians and forensic examinations for other purposes, explained Dr. Golen, Department of Ophthalmology, University of South Florida, Tampa.

He gave the example of abusive head trauma (previously termed "shaken baby syndrome") as a diagnosis that may potentially be aided or expedited with postmortem pupillary dilation.

TESTING THE PROTOCOL

In collaboration with the Lions Eye Institute for Transplant and Research (LEITR), Dr. Golen and colleagues tested a protocol for postmortem pupillary dilation and evaluated the effectiveness of topical mydriatic agents on fresh, non-preserved eye bank eyes. The investigators reviewed pre-death records that included patient demographics, medical and ocular histories, and medications, if available.

Dr. Golen

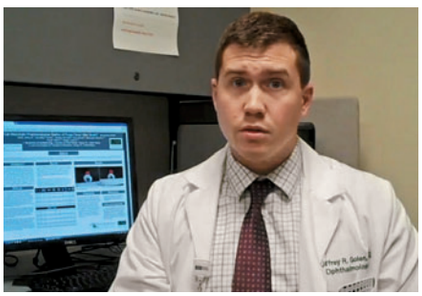
The eyes were also evaluated for iris color or other iris abnormalities. Initial ocular photographs were taken before dilation and focused on the pupillary margin. The photographs included a millimeter ruler placed near the eye. The investigators then placed two drops of a solution of 10% phenylephrine and 1% tropicamide on the corneal surface. These drops were repeated twice, 3 minutes apart.

In seven eyes, the drops were instilled before the eye was procured from the orbit and in another seven eyes after procurement. Similar photographs of the eyes were taken 20 and 60 minutes after drug application, again with the same millimeter ruler adjacent to the globe.

Dr. Golen measured the pupils in the photographs and recorded the diameters at the various time points for post-hoc analysis. Fourteen cadaver eyes of eight subjects (five women,

Continues on page 10 : ***Pupil dilation***

IN HIS OWN WORDS



VIDEO Pupils can be pharmacologically dilated after death, explains Jeffrey R. Golen, MD, Department of Ophthalmology, University of South Florida, Tampa. Go to **http://bit.ly/11031Sm** to see more. *(Video courtesy of Jeffrey R. Golen, MD)*

Special Report) **ARVO MEETING HIGHLIGHTS**

ARVO: Sight set on world-class science

Theme of 'life-changing research' provides current data on retina, glaucoma, dry eye, and more

From Ora Staff Reports; *Special to Ophthalmology Times*

SEATTLE ::

THOUGH THE SCENIC backdrop of the Pacific Northwest at this year's meeting of the Association for Research in Vision and Ophthalmology (ARVO) may have been different from the traditional Floridian seascape, the meeting's world-class science continues to be at the forefront.

Much like the anticipated Comparison of Age-related Macular Degeneration Treatments Trials last year, the scientific attraction of this year's meeting was the results of the Age-Related Eye Disease Study 2 (AREDS2) trial.[1] This 5-year study examining modifications to the original AREDS formulation included more than 4,000 participants, ages 50 to 85 years, who were at risk for advanced age-related macular degeneration (AMD). Although there was no overall benefit from adding omega-3 fatty acids or the antioxidants lutein and zeaxanthin to the original formulation, participants who were treated with both antioxidants without beta-carotene reduced their risk of AMD by approximately 18%.[2]

Editor's Note: For further information about AREDS2, see "AREDS gets another look," Ophthalmology Times, *June 1, 2013, Page 1).*

REFINING METHODS AND BEST PRACTICES

Novel data were presented on the use of software analysis for the evaluation of corneal superficial punctuate keratitis (SPK), an important primary endpoint for dry eye trials (*Rodriguez J et al. IOVS 2013;54: ARVO-E Abstract 4341)*. Although an automated approach is useful in standardizing the SPK evaluation process, it is not necessarily applicable in every situation, or for every disease. In a separate study, a software-based analysis of hyperemia grading showed that confounding factors in allergic hyperemia, such as chemosis, prevent the use of automated redness analyzers *(Raval Y et al. IOVS 2013;54: ARVO E-Abstract 2553).*

As ophthalmologists and vision scientists learn more and more about the diseases for which they spend their days developing drugs, they also know that refining and enhancing their methods for patient inclusion and disease assessment is an ongoing process. In the allergy arena, modifications to the traditional conjunctival allergen challenge protocol were used to elicit a more chronic, inflammatory conjunctivitis *(Gomes Pet al. IOVS 2013;54: ARVO E-Abstract 2555)*. Other improvements included updated protocols for fluorophotometry *(Heckley C et al. IOVS 2013;54: ARVO E-Abstract 6043)* and conjunctival staining *(Lane K et al. IOVS 2013;54: ARVO E-Abstract 6045)*.

Additionally, presentation topics ranged from best practices when deciding between blink rate and interblink interval *(Johnston P et al. IOVS 2013;54: ARVO E-Abstract 967)* and the importance of considering lid contact time to differentiate dry eye and normal subjects *(Lafond A et al. IOVS 2013;54: ARVO E-Abstract 962)*. Other presenters examined the relationship between tear meniscus dimensions and other disease measures in subcategories of dry eye and found that in patients with aqueous tear-deficient dry eye and autoimmune disease, lower tear volume is associated with worse corneal epithelial disease *(Tung CI et al. IOVS 2013;54: ARVO E-Abstract 970.*

The topic of advances in ocular surface microscopy was dominant as well. Studies of corneal nerve morphology (*Sanchez Dalmau BF et al. IOVS 2013;54: ARVO E-Abstract 530; You JY et al. IOVS 2013;54: ARVO E-Abstract 531)* by in vivo confocal microscopy (*IVCM*) demonstrated the utility of enhanced ocular-surface imaging. Other presentations focused on IVCM-based advances in limbal morphology *(Baclagon ER et al. IOVS 2013;54: ARVO E-Abstract 537)* and on inflammatory cell infiltration of the conjunctival vasculature (*Angeli E et al. IOVS 2013;54: ARVO E-Abstract 2557).*

EMERGING TREATMENTS FOR RETINAL DISEASE

A meta-analysis of ranibizumab safety data in patients with AMD, retinal vein occlusion (RVO), or diabetic macular edema (DME)

Continues on page 12 : ***Science***

PUPIL DILATION

(Continued from page 9)

three men; average age, 72.6 years) were included. The irises were brown in seven eyes, blue in six eyes, and hazel in one eye. No eyes had had apparent iris trauma, iris melanoma, evidence of iritis, or visible iridoschisis. Two subjects had a history diabetes mellitus, including one who was legally blind.

PUPILLARY DILATION RESULTS

Dilation was achieved in cadaver eyes up to 24 hours after time of death, Dr. Golen noted. Total pupillary dilation ranged from 0.7 to 2.6 mm in a heterogeneous group of unfixed tissue bank eyes, with a range of iris colors. Dilation also occurred across both study groups: those eyes with dilating drops applied after death but before procurement, and those eyes with dilating drops applied after procurement.

"Our group has developed a very simple protocol, which resulted in some degree of postmortem pupillary dilation in all 14 of the heterogeneous eyes studied," Dr. Golen said. "Knowledge of this phenomenon, as well as a simple protocol to attain it, is exciting and may be useful in many areas of ophthalmic research where ocular human tissue plays an essential role."

The effectiveness of the topical mydriatic agents on the bank eyes was likely aided by the prompt recovery and high quality of tissue provided by LEITR, Dr. Golen concluded. ■

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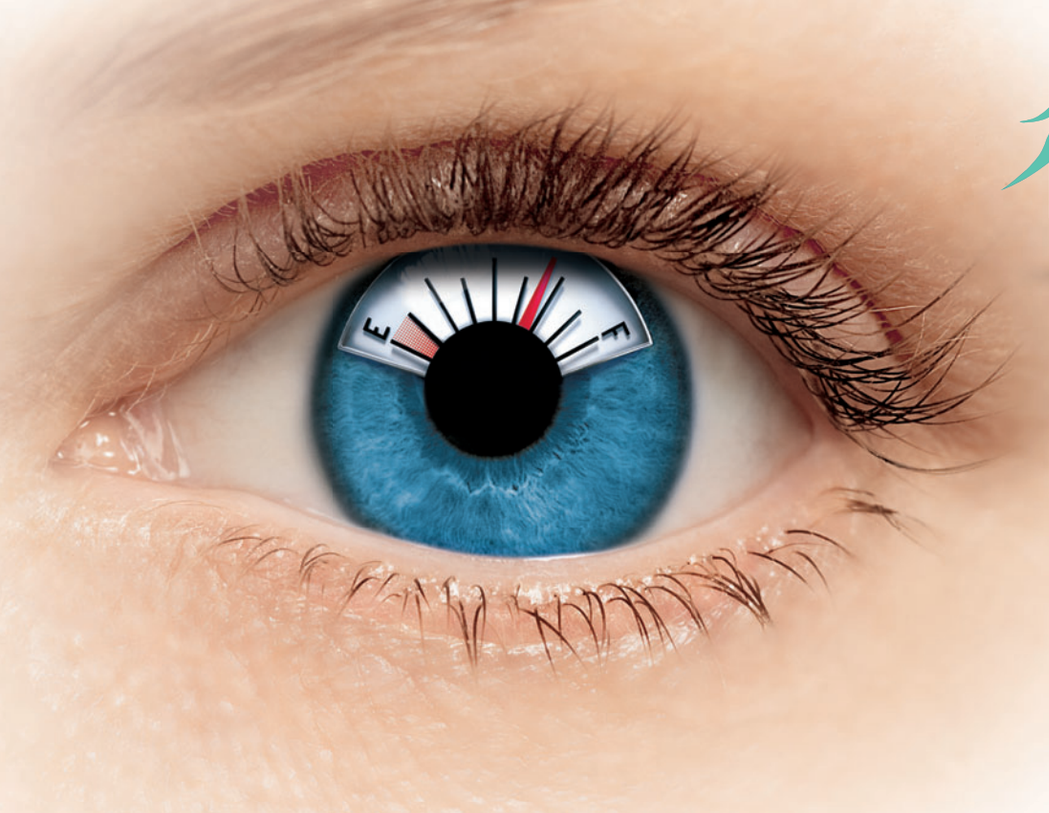
Dr. Golen has no financial interest in any aspect of this study. The Lions Eye Institute for Transplant and Research, Tampa, FL, sponsored and funded the study and provided the specimens.



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

ALLERGAN

SCIENCE

(Continued from page 10)

was also presented (*Avery RL et al. IOVS 2013;54: ARVO E-Abstract 1535)*. The analysis comprised 22 phase II, III, and IIIb studies and included 10,300 patients. After a mean follow-up time of 15.9 months, patients with DME showed higher mortality rates and greater rate of wound-healing complications than those with either AMD or RVO.

A phase III study subanalysis examined the efficacy of ocriplasmin (Jetrea, Thrombogenics NV) in traditional vitrectomy candidates (*Kuppermann BD. IOVS 2013;54: ARVO E-Abstract 1942)*. Overall, 33.2% of eyes treated with ocriplasmin achieved vitreomacular adhesion (VMA) resolution as compared with 11.5% of those treated with placebo.

take-home

No matter the setting, world-class science continues to be the focus at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO).

In vitro and in vivo data presented on AKB-9778 (Aerpio Therapeutics) confirmed its bioactivity as a potent and selective small-molecule inhibitor of vascular endothelial-protein tyrosine phosphtase (VE-PTP)(*Shen J et al. IOVS 2013;54: ARVO E-Abstract 6094)*. Although the drug is initially being developed for DME, vascular stabilization may also provide benefits for a number of diseases.

ALG-1001, a new small-molecule oligopeptide, is being investigated in a number of vascular eye diseases, including wet AMD, DME, and symptomatic VMA. Interim data on the phase Ib/IIa dose-ranging, monotherapy study targeting wet AMD were presented at this year's ARVO.[3,4] In this first-in-human study, the drug appeared safe and well tolerated, and a treatment effect was seen to last more than 4 months off-treatment. There was also a robust response in the 3.2-mg dose group of at least 3 months off-treatment in all subjects. A demonstrated mean best-corrected visual acuity improvement of +8 letters as measured by ETDRS in this group corresponded to a 30% decrease in central macular thickness and improvement in retinal architecture.

A LOOK AT GLAUCOMA THERAPIES

Amakem Therapeutics presented new preclinical data on its frontrunner, the locally acting Rho-kinase (ROCK) inhibitor, AMA0076. In Dutch Belted rabbits, once-daily treatment with AMA0076 resulted in IOP reduction that was more sustained than Y-39983, a non-local ROCK inhibitor (*Van de Velde S et al. IOVS 2013;54: ARVO E-Abstract 5631)*. This data was much anticipated after an abundance of presentations on the drug at last year's ARVO (*Van de Velde S et al. IOVS 2012;53: ARVO E-Abstract 1977; Sijnave D et al. IOVS 2012;53: ARVO E-Abstract 2522; Hollanders K et al. IOVS 2012;53: ARVO E-Abstract 1974*).

Data implicating β-Amyloid in the pathology of glaucoma in human glaucomatous retinae in comparison with healthy subjects (*von Thun und Hohenstein-Blaul N et al. IOVS 2013;54: ARVO E-Abstract 1139*) puts MRZ-99030, a β-Amyloid aggregation modulator, at the forefront of potential glaucoma therapies. In a rodent model of glaucoma, the topically administered drug dose-dependently and significantly reduced retinal ganglion cell apoptosis compared with vehicle control (*Gravius A et al. IOVS 2013;54: ARVO E-Abstract 2625)*.

ONO-9054, an isopropyl ester derivative of the free acid ONO-AG-367, was the focus of several abstracts. The dual FP/EP3 receptor agonist may be effective in lowering IOP (*Yamane S et al. IOVS 2013;54: ARVO E-Abstract 766; Karakawa T et al. IOVS 2013;54: ARVO E-Abstract 1998)*. In a double-masked study of

Although there are a variety of assessments for assessing tear film stability, **there has been no consensus on which combination of tests should be used to define the dry eye.**

healthy volunteers, ONO-9054 was well tolerated and there was no apparent dose-related responses in any of the tolerability parameters (*Rower-Rendleman C et al. IOVS 2013;54: ARVO E-Abstract 440)*.

TEAR FILM STABILITY AND OCULAR SURFACE DISORDERS

Although there are a variety of assessments for assessing tear film stability, there has been no consensus on which combination of tests should be used to define the dry eye. Saigal et al. presented data on the correlations of dry eye signs to signs, symptoms to symptoms, and both to objective tests of tear film stability. The authors reported the correlation of many signs and symptoms and quality-of-life variables, contrary to many reports that suggest otherwise (*Saigal S et al. IOVS 2013;54: ARVO E-Abstract 4361)*.

Mimetogen presented post-hoc data from a completed trial of MIM-D3 ophthalmic solution, which targets mucin-protective compensatory mechanisms. Patients with greater or more rapid exacerbation of signs and symptoms from the controlled adverse environment were more responsive to MIM-D3 (*Ousler G et al. IOVS 2013;54: ARVO E-Abstract 4343)*. Additional post-hoc analyses support an association between the duration of dry eye and the response to treatment for the reduction in both signs and symptoms (*Meerovich K et al. IOVS 2013;54:ARVO E-Abstract 4340)*.

Eleven Biotherapeutics presented clinical data from a phase I safety study demonstrating that EBI-005 was safe and well-tolerated in normal volunteers at two dose levels (*Goldstein M et al. IOVS 2013;54: ARVO E-Abstract 4319)*. EBI-005 is a potent IL-1R1 inhibitor. Preclinical toxicology data set the stage for success, as it demonstrated that EBI-005 was well tolerated in both mouse and rabbit models (*Furfine E et al. IOVS 2013;54: ARVO E-Abstract 4320)*.

Shifting gears to the up-and-coming notion of re-purposing agents, two poster presentations highlighted the use of low-dose brimonidine as an eye whitener *(Chapin MJet al. IOVS 2013;54: ARVO E-Abstract 2556; Horn G et al. IOVS 2013;54: ARVO E-Abstract 5451*).

Last, but not least, pre-clinical data on a new topically administered anti-inflammatory, cis-urocanic acid, demonstrated a significant reduction in corneal staining using a murine model of dry eye (*Whitlock A et al. IOVS 2013;54: ARVO E-Abstract 902)*. It also showed promise in a preclinical study of allergic conjunctivitis (*McLaughlin J et al. IOVS 2013;54: ARVO E-Abstract 2554)*. ■

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Faces detected with retinal prosthesis

SEATTLE ::

NEW DATA SHOW THAT A RETINAL PROSTHESIS SYSTEM is capable of providing face detection functionality to blind individuals, said Paulo E. Stanga, M, at the annual meeting of the Association for Research in Vision and Ophthalmology.

The approved device (Argus II Retinal Prosthesis System, Second Sight) is intended to restore some functional vision for people who have lost their sight.

The question we asked was if faces can be detected with a retinal prosthesis, said Dr. Stanga, professor of ophthalmology and retinal regeneration at the University of Manchester, England.

"In the normal use of retinal prostheses, facial detection is limited by a number of factors," Dr. Stanga said. "Many Argus II users have had difficulty distinguishing faces from other similar sized and shaped objects."

Approved by the FDA in February, the device can provide electrical stimulation of the retina, which, in turn, induces visual perception in blind individuals with retinitis pigmentosa. The system can provide visual capabilities to those currently unable to see anything except perhaps extremely bright lights.

To address question of facial recognition, two experiments were conducted by Dr. Stanga and colleagues to evaluate if device users can locate human faces with their systems using a facial detection algorithm and if this the speed of detection would be improved if changes were made to the field of view that is mapped onto the Argus implant.

They used two different magnifications. The image-processing algorithm captured a field-of-view that matched the field-of-view of the implanted array (20° diagonally) while for others, the entire field-of-view of the camera (53°) was captured and "zoomed out" to fit the array. The time to locate the "target" was significantly shorter when the wider field-of-view was used.

"Faces were detected and localized in 100% of the trials," Dr. Stanga said. "Each patient went through ten trials."

In the second experiment, they looked at facial detection in a real-world setting, and if during a conversation, a user could determine when eye contact is lost.

"Both subjects detected the loss of eye contact 100% of the time," Dr. Stanga said. "The time was 5.5 seconds and 6.4 seconds."

Therefore, they concluded that this feasibility study was able to demonstrate that image-processing algorithms can enable device users to perform daily tasks that are not limited by the resolution or the sensitivity of the array. ■

Special Report 〉 **ARVO MEETING HIGHLIGHTS**

Managing DME for the long haul

Truck drivers navigate health, financial impact of diabetes and diabetic macular edema

By Lynda Charters; *Reviewed by Sunil S. Patel, MD, PhD*

SEATTLE ::

MANAGING DIABETES IS a substantial burden for long-haul truck drivers who may be susceptible to diabetic macular edema (DME).

Most problematic is that current commercial driver license (CDL) requirements prohibit use of insulin by drivers. Health-care providers are challenged by this issue when they develop programs to improve outcomes among patients with diabetes.

"For truck drivers, diabetes management is difficult because of the limited healthy-food choices on the road, limited opportunities to exercise, and the unwillingness to start insulin therapy due to regulations surrounding commercial vehicle operation and insulin use," said Sunil S. Patel, MD, PhD, at the annual meeting of the Association for Research in Vision and Ophthalmology.

In addition, truck drivers' ability to remain in their profession depends on good vision, he noted.

take-home

- **Vision loss caused by diabetic macular edema increases the health and financial burdens of managing diabetes, especially for long-haul truckers who rely on their eyesight to maintain employment.**

FOCUS GROUPS AND COST DIARIES

Dr. Patel and his colleagues hypothesized that DME creates a substantial economic burden for truck drivers and payers. To prove the hypothesis, they formed focus groups and used cost diaries to explore the related problem. Patients were recruited from the West Texas Retina Consultants, a private practice in Abilene, TX, where Dr. Patel practices. Patients who agreed to participate in the study were assigned to one of two focus groups (i.e., former truck drivers and current truck drivers).

Dr. Patel

The focus groups met for 90 minutes and an experienced moderator led the discussions. Participants then completed a 90-day diary to record out-of-pocket expenses related to diabetes. They also recorded the time that they and their caregivers spent on activities related to diabetes or diabetes-related vision care.

Eight patients of 26 who were contacted agreed to participate in the study; four were current drivers and four were former drivers who could no longer driver because of decreases in visual acuity. Themes that were identified based on the focus group discussions were direct and indirect costs, vision and driving, diabetes and driving, mental health, and licensing.

Seven participants returned completed daily diary pages over the entire 90 days.

The investigators found that the mean total annual out-of-pocket cost for diabetes and DME-related care was $4,743, with the greatest costs for vision aids ($2,801). Travel ($297), medications ($845), medical services ($634), and other services ($166) were the other considerations.

Direct medical costs were an additional expense for catastrophic diabetes-related events for two participants, one of whom underwent toe amputation with a systemic infection and the second, kidney failure.

The mean annual time for diabetes- or vision-care-related activities was 36 hours for patients and 92 hours for caregivers.

Problems that drivers specifically mentioned were the higher costs of healthier foods, severe night-driving problems, the psychological impact of visual acuity loss, and the inability to have another job.

Representative comments were:

> **"It is expensive to have diabetes, not just your medication and your testing supplies, but the kind of foods that you need to eat. You know, can't buy a 50-cent pizza and put it in the oven, because 2 hours later, you're back there with a blood sugar [reading] of 400."**

> **"The night driving when you have this is much worse, because when you have . . . retinopathy, your vision is already compromised. But at night, when you've got those headlights coming at you . . . I caught myself several times heading toward . . . the vehicle that was coming at me."**

Measuring health-benefit costs, missed work

IN A RELATED study, Sunil S. Patel, MD, PhD, and colleagues conducted a retrospective analysis of the HCMS Group's research reference database to compare annual health-benefit costs and absenteeism among commercial drivers and non-driver U.S. employees with diabetic macular edema (DME), diabetic retinopathy (DR), diabetes, or employees without diabetes. The study found that health-benefit costs for drivers with DME were three times higher compared with employees without DME, DR, or diabetes. Drivers with DME missed 27 days of work annually compared with those without the condition, who only missed 8 days.

It is hoped by the researchers that the analysis will provide employers with the necessary information to assess the impact of DME and DR on employees, and provide insight into the importance of treatment for these conditions. This study was presented during the American Diabetes Association's 73rd Scientific Sessions in June.

SUMMARIZING THE ISSUES

"Diabetes and DME create significant economic burdens for truck drivers," Dr. Patel concluded. "Current CDL requirements—such as those that prohibit insulin use—may deter patients from properly controlling blood sugar levels, which can result in expensive diabetes-related medical events.

"Health-care providers may want to consider these issues as they develop programs to improve outcomes among patients with diabetes," he added. ■

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Genentech sponsored both studies.

Why slow-release ocular therapy for AMD, DME may be on horizon

Hydrogel depots could result in fewer yearly intravitreal injections, side effects

By Lynda Charters; *Reviewed by Rami El-Hayek, PhD*

Figure 1: Tunable Release of Ovalbumin from Hydrogels

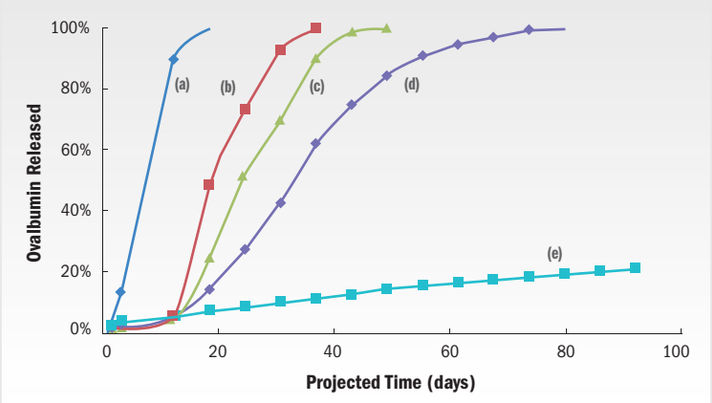
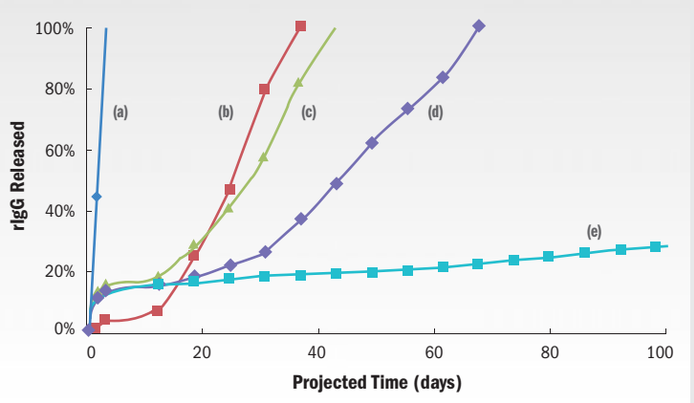


Figure 2: Tunable Release of Rabbit IgG from Hydrogels



Release profiles of ovalbumin (OVA) and rabbit immunoglobulin G (rIgG) show the effect of hydrogel degradation time on sustained release of OVA and rIgG. A comparison of OVA and rIgG release using the same hydrogels indicates that rIgG is released more slowly than OVA due to the difference in molecular size. *(Figures courtesy of Rami El-Hayek, PhD)*

SEATTLE ::

THE SLOW RELEASE OF protein-based drugs presents a difficult formulation challenge due to the fragile nature of their molecular structure, such as vascular endothelial growth factor (VEGF) inhibitors.

Studying the release rates of surrogate proteins or antibodies—such as ovalbumin (OVA) and rabbit immunoglobulin G (rIgG)—from hydrogel depots may signify viability of the sustained-release technology for long-term, anti-VEGF therapies to treat retinal diseases, such as age-related macular degeneration (AMD) and diabetic macular edema (DME), explained Rami El-Hayek, PhD, at the annual meeting of the Association for Research in Vision and Ophthalmology.


Dr. El-Hayek

Though frequent intravitreal injections of anti-VEGF drugs can manage progression of these diseases to prevent vision loss—and, in some cases, increase visual acuity levels—frequent intravitreal injections are associated with increased risks of infection, retinal detachments, and hemorrhages, and carry a substantial financial and time burden for patients. Sustaining the delivery of such drugs over extended periods, resulting in fewer injections and lower risks to patients, could be a breakthrough therapy in ophthalmology and would be easily applied in other areas where high-molecular, weight-active pharmaceutical ingredients need to be delivered over months versus days or weeks.

INJECTABLE HYDROGEL DEPOTS

Dr. El-Hayek and his colleagues at Ocular Therapeutix conducted a study to evaluate the sustained release of OVA and rIgG in vitro from pre-formed injectable hydrogel depots with variable degradation times. Fine particles of the two substances were formulated with hydrolytically degradable synthetic poly(ethylene glycol) hydrogels to form degradable depots.

The depots were examined in vitro for sustained release under accelerated conditions. The concentrations of OVA and rIgG were determined by high-performance liquid chromatography. A comparison of the release of OVA and rIgG using the same hydrogels showed that rIgG was released more slowly than OVA because of differences in the sizes and molecular weight of the molecules. It should be noted that OVA and rIgG released over 3 to 6 months still preserved their structure and stability and did not aggregate.

"Rapidly or slowly degrading hydrogel formulations can be tailored for different drug-release rates and durations required by specific therapies covering a range of therapy release times extending to 6 months and even longer," Dr. El-Hayek said.

In this study, hydrogels made using non-degradable linkages used as controls reach maximal release after diffusion of surface and free particles, but still held the OVA and rIgG particles over a long duration, thus demonstrating that the hydrogel degradation regulated release.

MORE CONVENIENT THERAPIES

This proprietary technology seems to be a major step toward more convenient therapies for posterior segment diseases. The ability to individualize the release of OVA and rIgG from hydrogel depots for sustained delivery of proteins could provide a technology platform that can be used with anti-VEGF therapies to reduce the number of yearly intravitreal injections and potentially reduce the risk of side effects, Dr. El-Hayek concluded. ■

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Dr. El-Hayek is an employee of Ocular Therapeutix.

Special Report) **ARVO MEETING HIGHLIGHTS**

How emixustat hydrochloride may help geographic atrophy

Drug modulates visual cycle activity, reduces oxidative stress, slows accumulation of toxins

By Lynda Charters; *Reviewed by Pravin U. Dugel, MD*

SEATTLE ::

EMIXUSTAT HYDROCHLORIDE (ACU-4429, Acucela/Otsuka Pharmaceutical) may be a breakthrough in research for geographic atrophy in dry age-related macular degeneration (AMD).

This drug modulates visual cycle activity, reduces oxidative stress, and slows accumulation of vitamin A-based toxins. The drug appears safe and well tolerated with few serious adverse events, noted Pravin U. Dugel, MD, at the annual meeting of the Association for Research in Vision and Ophthalmology.

The non-retinoid small molecule is administered orally and inhibits activity of RPE65 to reduce the rate of vitamin A processing in the visual cycle. The specific activities include reducing vitamin A toxins, reducing the metabolic rate of the photoreceptors, and protecting the retina from light damage.

By inhibiting RPE65 activity, the visual cycle is slowed and production of A2E is reduced.

"Reduction of A2E would then theoretically slow progression of retinal pigment epithelial membrane damage, free radical production, increase inflammation, and the resulting contribution to the progression of dry AMD and geographic atrophy," said Dr. Dugel, managing partner, Retinal Consultants of Arizona, Phoenix, and clinical associate professor of ophthalmology, Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles.

Dr. Dugel

take-home

Treatment with emixustat hydrochloride may be useful for treating geographic atrophy by modulating visual cycle activity, reducing oxidative stress, and slowing accumulation of vitamin A-based toxins.

ENVISION CLARITY TRIAL

A phase II multicenter, randomized, placebo-controlled, double-masked, multidose study (ENVISION Clarity Trial) evaluated emixustat hydrochloride (2, 5, 7, or 10 mg once daily in the morning, or 5 mg once daily at bedtime) versus placebo once daily (3:1 ratio) to assess the safety, tolerability, and pharmacodynamic effects (measured by dark-adapted electroretinography [ERG]) over 3 months.

Inclusion criteria included the presence of geographic atrophy, steady fixation and clear media to allow fundus visualization, and a best-corrected visual acuity of 20/400 or better in the study eye.

Seventy-two subjects were randomly assigned to one oral daily dose of emixustat hydrochloride or placebo for up to 90 days. Adverse events and other safety parameters were collected. ERGs were recorded 30 minutes after dark adaptation. The eyes were photobleached and ERGs were recorded immediately and at 10, 20, and 30 minutes. Rod b-wave amplitudes were expressed as a percentage of the pre-bleach, dark-adapted rod amplitude from baseline. The rate of rod recovery (slope) for each emixustat hydrochloride group was compared with the placebo group.

COMMON OCULAR ADVERSE EFFECTS

In patients treated with emixustat hydrochloride, rod b-wave amplitude suppression (a measurement of rod activity) was dose-dependent, Dr. Dugel noted. In addition, the effects seemed to plateau by day 14. The pharmacologic effect was reversible when the drug was stopped and returned to the baseline level after 1 to 2 weeks off the study drug in all dosage groups.

Chromatopsia and delayed dark adaptation were the most common ocular adverse effects. Visual impairment also occurred in some patients.

"Moderate chromatopsia occurred in all treatment groups," Dr. Dugel said. "It started as early as day 2 and as late as day 52. The effects were intermittent or continuous and varied from 3 hours to 51 days. Two patients in the 5-mg group terminated treatment early because of serious chromatopsia. Fifty percent of patients had mild or moderate chromatopsia that resolved before the end of the study. In the 5-mg group, 10 of the 19 chromatopsia events were 7 days or shorter in duration."

Moderate delayed dark adaptation (intermittent or continuous) began as early as day 3. One patient receiving the 5-mg dose ended treatment early because of serious chromatopsia. Overall, mild and moderate delayed dark adaptation resolved in 25% of patients by the end of the 90-day study. Delayed dark adaptation was expected, Dr. Dugel noted, because of the drug's mechanism of action. Emixustat hydrochloride slows rod cell function, and because rods are responsible for sight in low-light conditions, delayed dark adaptation may result, he explained.

Moderate visual impairment (intermittent or continuous) occurred in the 2-, 7-, and 10-mg treatment groups. They initiated as early as day 2 and as late as day 48. The episodes varied in duration from 3 minutes to 37 days. Overall, 95% of cases of mild and moderate visual impairment that resolved before the end of the study.

"This dose-escalation study of 72 patients with geographic atrophy showed no significant systemic adverse events and the drug was generally safe and well-tolerated," Dr. Dugel summarized. "Most drug-related adverse events were ocular with mild to moderate severity and started within 2 weeks of dosing and resolved during the 90-day study. There was potential for a reduced incidence of chromatopsia with evening dosing."

A long-term phase IIb/III study is under way to evaluate emixustat hydrochloride in patients with geographic atrophy. ■

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Special Report 〉 **ARVO MEETING HIGHLIGHTS**

Integrin peptide for AMD emerging

Improvements persisted for 60 days off-treatment after three monthly loading doses

By Roxanne Nelson; *Reviewed by Peter K. Kaiser, MD*

SEATTLE ::

INTEGRIN PEPTIDE THERAPY is an emerging new class of treatment for neovascular eye diseases, including wet age-related macular degeneration (AMD).

In the first clinical trial of a synthetic anti-integrin oligopeptide (ALG-1001, Allegro Ophthalmics) in wet AMD, there was an apparent clinical benefit to patients, as evidenced by improvements from baseline visual acuity and macular anatomy, said study author Peter K. Kaiser MD, at the annual meeting of the Association for Research in Vision and Ophthalmology.


Dr. Kaiser

Despite the fact that this was a phase Ib trial with a small study cohort, the authors note that clinically relevant indicators of efficacy were demonstrated with improvements in best-corrected visual acuity (BCVA) alongside anatomic improvements in optical coherence tomography (OCT) central macular thickness (CMT). These improvements persisted for at least 60 days off-treatment after receiving three monthly loading doses.

"The study is . . . ongoing with a handful of study subjects still finishing . . . their last few visits," said Dr. Kaiser, a staff member of the vitreoretinal faculty of the Cole Eye Institute, Department of Ophthalmology, Cleveland Clinic. "The improvements in BCVA and macular anatomy appear to hold past 3 months off-treatment."

To date, the longest follow-up time is 5 months off-treatment. That was for one participant who returned a month late for the 4-month off-treatment visit.

"The study subject was still holding BCVA and anatomic improvements at 5 months off all treatment," Dr. Kaiser said.

HOW IT WORKS

ALG-1001 interferes with several pathways of the angiogenic cascade, as it can bind to multiple integrin-receptor sites that are known to be involved in both choroidal and pre-retinal neovascularization. In vitro, ALG-1001 inhibits integrin receptors and in vivo, arrests aberrant blood vessel growth that is meditated by integrins αv β3, αv β5, and α5 β1.

These are sites that are expressed in neovascular ocular tissue in wet AMD as well as diabetic retinopathy.

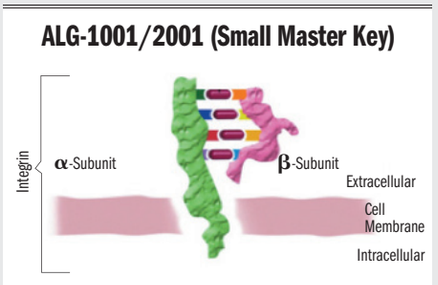
Experimental studies showed a statistically significant reduction in choroidal neovascularization (CNV), retinopathy of prematurity (ROP), and vascular permeability. A small phase I study in patients with diabetic macular edema showed that more than half of cohort (55%) improved 3 to 5 lines in BCVA, with at least a 30% reduction in OCT CMT with ALG-1001 monotherapy that held for at least 3 months off-treatment.

PHASE IB TRIAL

In this phase Ib trial, Dr. Kaiser and colleagues evaluated the safety and dose ranging of intravitreal ALG-1001 in patients with CNV due to wet AMD. The primary endpoint of the study was to observe any dose limiting toxicity.

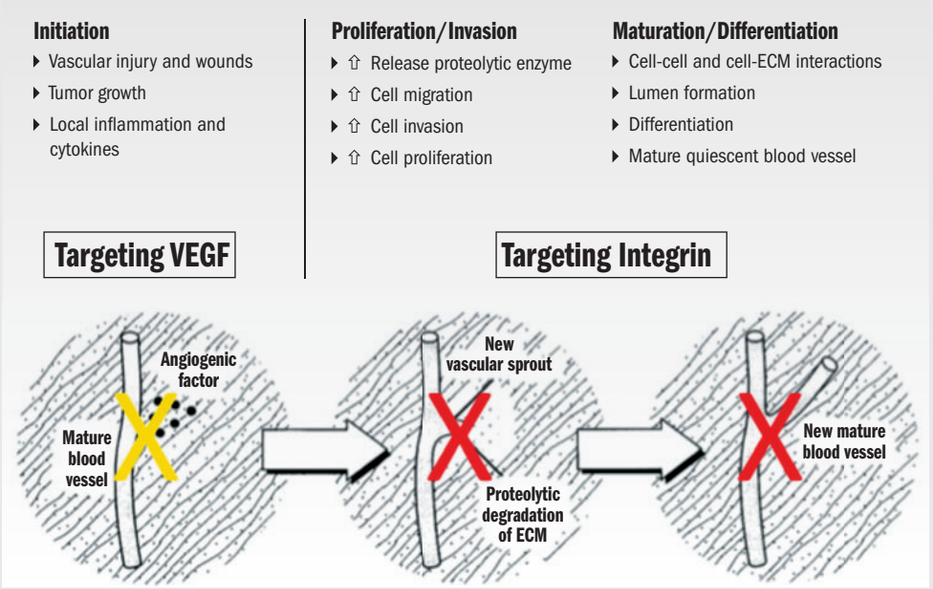
The key criteria for trial inclusion included a baseline BCVA between 20/50 and 20/320 and CNV due to AMD, and patients could not have received prior treatment with anti-vascular endothelial growth factor (VEGF) treatment within 45 days of enrollment. The 15 participants who have been in enrolled in the

Binds to Multiple Integrin-Receptor Sites

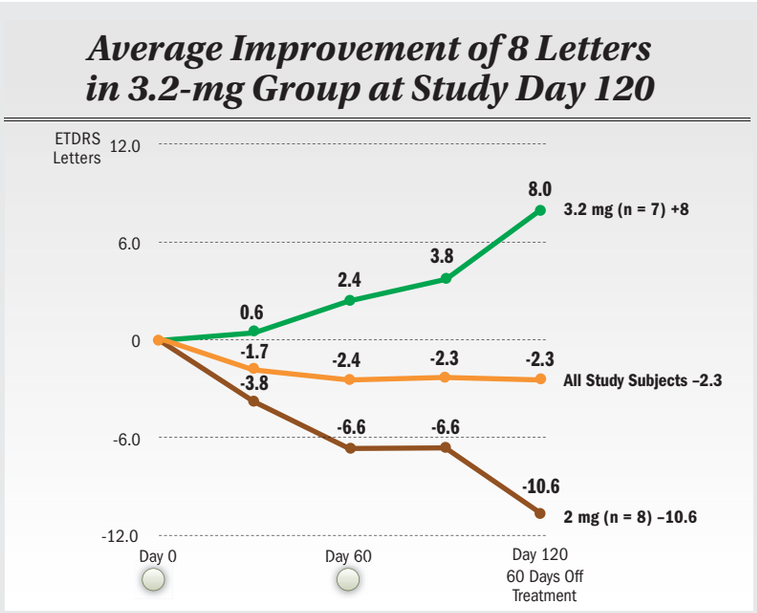


(Figure 1) Unlike monoclonal antibodies, ALG-1001 is a small oligopeptide capable of binding to multiple integrin-receptor sites with a long-lasting effect.

ALG-1001 Targets Key Integrin-Receptor Sites



(Figure 2) Working from a different mechanism of action from anti-vascular endothelial growth factor therapy, ALG-1001 targets key integrin-receptor sites implicated in proliferation and maturation of new blood vessels.



(Figure 3) A dose response curve shows patients in the 3.2-mg group responded with an average improvement of 8 letters, whereas there was a continued loss of vision on average with the 2-mg group. *(Figures courtesy of Allegro Ophthalmics)*

trial are a combination of treatment-naïve and previously treated patients.

All patients received a loading dose of three monthly intravitreal injections of either 2- or 3.2-mg ALG-1001 in monotherapy and were followed for an additional 4 months off-treatment.

Even though it was not the primary endpoint of the study, and the study continues to be ongoing, the authors observed that there was a clear improvement in BCVA and macular anatomy by OCT in about 50% of trial participants in the 3.2-mg dose group. These clinical benefits were long lasting and persisted for at least 60 days off-treatment, following a three-monthly-injection-loading dose.

There was a definite dose response curve between the 2- and the 3.2-mg doses, Dr. Kaiser noted.

"The higher 3.2-mg dose produced a robust clinical response/improvement," he said. "The average improvement in ETDRS BCVA was +8 letters in the 3.2-mg dose at study day 120, which was 60 days off-treatment after the three monthly loading doses."

In addition, the mean reduction in central macular thickness for group receiving 3.2 mg was 29.8% at study day 150, which was 90 days off-treatment after the three loading doses.

"And these results were for monotherapy with the ALG-1001 drug, not combination therapy," Dr. Kaiser said.

Clinical benefits of ALG-1001 lasted for at least 60 days after treatment ended, but it is unknown how long patients would have to continue using the agent in order for benefits to continue. The exact duration of the clinical benefit is unknown at this time.

take-home

- **In the first clinical trial of ALG-1001 in wet AMD, there was an apparent clinical benefit to patients, as evidenced by improvements from baseline visual acuity and macular anatomy.**

But based on these results, Dr. Kaiser believes that this is a promising new treatment for this patient population.

"We were very happy to see such a strong efficacy signal in a phase I, proof-of-concept study, with the clinical benefits holding on average out to at least 90 days off-treatment," he said. "Given this drug's different mechanism of action, over anti-VEGF and the early but robust efficacy signal generated in this study, it gives us hope that this drug will provide a new category of long-lasting drugs to treat the large patient population affected by wet AMD."

The authors are planning a phase II U.S. study in wet AMD that will look at dose ranging, dosing regimens, and ALG-1001 used as monotherapy, and as part of combination therapy. ■

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Dr. Kaiser did not indicate a proprietary interest in the subject matter. Allegro Ophthalmics is developing this compound.

Special Report 〉 **ARVO MEETING HIGHLIGHTS**

Estrogen, POAG link explored

Gender-specific study finds variations in estrogen levels play role in glaucoma risk

By Cheryl Guttman Krader; *Reviewed by Louis R. Pasquale, MD*

SEATTLE ::

COMMON VARIANTS IN estrogen metabolizing genes collectively contribute to primary open-angle glaucoma (POAG) in women, according to researchers at the annual meeting of the Association for Research in Vision and Ophthalmology.

Dr. Pasquale

Louis R. Pasquale, MD, and co-workers investigated associations between the disease and a panel made up of about 900 single-nucleotide polymorphisms (SNPs) from the estrogen metabolism pathway using samples from more than 6,600 patients with POAG and unaffected controls. Using sophisticated software to perform complex analyses, no associations were found between the estrogen SNP pathway and POAG overall, high-pressure glaucoma (IOP ≥22 mm Hg) or normal-pressure glaucoma (IOP <22 mm Hg) when looking at the entire study population.

However, when the study group was divided by gender, an association was found between the estrogen SNP pathway and POAG in women. Findings from an IOP-based subgroup analysis showed the association in women was only with high-pressure glaucoma.

"The findings from this study provide additional support for the concept that variations in estrogen levels play a role in glaucoma risk," said Dr. Pasquale, HMS Distinguished Ophthalmology Scholar and associate professor of ophthalmology, Harvard Medical School, Boston. "As a next step, we hope to establish that estrogen levels are different [when] comparing women who go on to develop open-angle glaucoma (OAG) and those who do not, as that would provide definitive evidence that declining estrogen levels are important in determining a woman's risk for developing OAG."

Currently, Dr. Pasquale is writing a grant application to the NIH for a case-control study that would use banked blood and participant data from the Nurses' Health Study (NHS) to compare circulating estrogen levels in women with and without glaucoma while taking into account menopause status, type (natural or surgical), and use of hormone replacement therapy.

BUILDING THE ESTROGEN STORY

Interest in investigating a role of circulating estrogen in the pathogenesis of glaucoma derives from several observations, beginning with the fact that estrogen receptors are present on retinal ganglion cells. In addition, studies have shown IOP decreases during pregnancy and in postmenopausal women using hormone replacement therapy. There is evidence that neuroretinal rim thickness as well as visual field performance vary as a function of the menstrual cycle.

In addition, analyzing NHS data, Dr. Pasquale and co-workers previously reported an increased risk of POAG among women using oral contraceptives for 5 or more years but a reduced risk of the high-tension variant in women with menopause onset at a later age. Consistent with the latter finding, Dutch researchers found that early-age menopause was associated with an increased risk of OAG. In an Australian study, investigators found the incidence of OAG in women lagged behind that of men during the 5th and 6th decades of life and caught up thereafter, consistent with the idea that women were protected early after menopause by waning estrogen levels.

Previous studies have also investigated whether a genetic component might explain variations in declining estrogen levels and glaucoma risk, but they yielded conflicting results, noted Dr. Pasquale, who is also director of the glaucoma service, Massachusetts Eye and Ear Infirmary, Boston.

"However, the prior studies did not look at a full complement of estrogen metabolizing genes," he said.

To address the latter limitation, Dr. Pasquale's colleague, Stephanie Loomis, BA, MPH, glaucoma genetics research coordinator, Massachusetts Eye and Ear Infirmary, Boston, conducted a thorough literature search to identify enzymes responsible for controlling circulating estrogen levels. Her review found 23 genes on 15 chromosomes and a total of 903 common variants of those genes that were used for the analyses in the present study.

IMPLICATIONS FOR IMPROVED CARE

In the future, Dr. Pasquale expects it will be possible to develop a genomic-based risk calculator for predicting the likelihood that a woman will develop POAG. Such a tool will depend on the identification of at least 50 genes that contribute to glaucoma risk, he said.

"So far, we have identified only a handful of associated genes, but we expect that number to double soon and firmly believe that we will be using genetic information to identify susceptibility to POAG in women in the future," he said.

Knowledge about genes associated with glaucoma development can also open the door to new understanding of disease pathogenesis and the identification of novel therapeutic targets. For example, the finding that polymorphisms in the gene for catechol-O-methyl transferase had the strongest association with POAG suggests the possibility that a topical therapy modulating the activity of this gene or the enzyme itself might be effective for reducing the likelihood of glaucoma development in at-risk women or as a treatment for early or moderate disease. ■

take-home

- **Data analyses found a strong association in women between estrogen metabolism pathway single-nucleotide polymorphisms and high-pressure, open-angle glaucoma.**

What are your thoughts? Weigh in on the findings of this gender-specific analysis at **Facebook.com/OphthalmologyTimes**.

LOUIS R. PASQUALE, MD

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Dr. Pasquale did not indicate a proprietary interest in the subject matter.

IN THE EXAM ROOM
Thomas Gosling, OD, evaluates candidates who could benefit from anti-eyestrain lenses. Dr. Gosling uses a +1 D flipper over the patient's best-corrected distance prescription, while the patient views his or her smartphone, tablet, or ideally, a backlit digital device. *(Photo courtesy of Thomas Gosling, OD)*

ANTI-EYESTRAIN LENSES

Optical solutions in a high-tech world

Why accommodative demand is rising in wake of increased use of smartphones, tablets

By Renee Jacobs, OD, MA

As the world embraces handheld technology, such as smartphones and tablet computers, many individuals suffer ocular side effects. The symptoms, common to computer vision syndrome, include dry eyes, tired eyes, and blurry vision. To put it bluntly, eyeballs simply cannot adapt as fast as smartphones can evolve. Accommodative demand is increasing.

Clearly, handheld tools carry tremendous benefits for patients. They can check e-mail while in the waiting room, video-record physicians as they provide medical and prescription advice during their eye examination, scan bar codes and photograph frames in the optical dispensary for comparison shopping, and tweet about the experience with their friends.

The downside of handheld tools is that they have side effects, too. With so much attention, literally at the fingertips, even young people experience accommodative symptoms. For these individuals, from grade school to young professionals, anti-eyestrain lenses offer a comfortable alternative to traditional single-vision lenses. Furthermore, business leaders can embrace this growing class of lenses as a revenue opportunity.

Continues on page 22 : ***Eyestrain***

TAKE-HOME

- ***Though handheld technologies carry tremendous benefits for patients, the downside is that they come with side effects—dry eyes, tired eyes, and blurry vision. For patients with accommodative symptoms, lenses that counter the effects of eyestrain offer a comfortable alternative to traditional single-vision lenses.***

In Brief

FROM STAFF REPORTS

Star power

ARTISTIC STYLE LEADS NEW ZYLOWARE RELEASES

PORT CHESTER, NY :: **ZYLOWARE HAS INTRODUCED** new styles from Daisy Fuentes Eyewear.

The Daisy Fuentes Carla (below) is a full-rim handcrafted zyl frame. The zyl temples are embellished with a foil animal print design. Spring hinges enhance the comfortable fit. Colors: tortoise/pink (shown), black/white.

New in the Etched collection is the XP 601M for men (above), designed with a thin, full-rim metal front and a sleek, wrapping metal endpiece. Thick, handcrafted zyl temples feature a metal plaque with a unique inlay pattern. For enhanced comfort, the XP 601M has spring hinges, snap-in nosepads, and accommodates progressive lenses. Colors: dark gunmetal (shown), brown.

Extra magnification

MAGNIFIERS ADD +5 D FOR FOCUSING AT NEAR

GROVER BEACH, CA :: **DR. HIRSCH'S MAGNIFYING** Spectacles from Marlin Industries enable practitioners to provide their patients with an additional +5 D associated with base-in prism for focusing at an 8-inch distance.

The magnifiers are made from optical-grade polycarbonate with a scratch-coated front. They maintain excellent memory even when stretched over the widest of frames.

These spectacles are well suited for visually compromised and normally sighted patients for many vocational and avocational needs that often require extra magnification at near.

EYESTRAIN

(Continued from page 21)

Recently, I met an optometrist who is excited about anti-eyestrain lenses. Thomas Gosling, OD, is an independent optometrist who has become highly skilled at identifying candidates who could benefit from anti-eyestrain lenses. He has developed a "show-and-tell" presentation for the exam room so that patients can feel comfortable before they buy. Dr. Gosling's practice is in Littleton, CO; however, patients from around the United States come to see him.

TARGET MARKET

For years, we have known that pre-presbyopia begins at birth. The crystalline lens adds layers throughout our lifetime. In the past, patients were labeled as having presbyopia when they became symptomatic enough to accept add power, typically in their 40s.

Now, we are realizing that patients with pre-presbyopia can benefit from assistance at younger ages, sometimes as early as grade school or college.

Eye-care professionals (ECPs) should look for the patients who complain of intermittent blur, tired eyes, headache, eyestrain, fatigue, and lack of mental focus. Dr. Gosling uses two methods to identify these patients:

METHOD 1

MEDIA-USE QUESTIONNAIRE

Add media-use questions to the current medical history questionnaire, toward better understanding accommodative demand due to lifestyle. Begin a discussion about symptoms.

METHOD 2

BEHAVIOR IN THE EXAM ROOM

Dr. Gosling uses a 1 D flipper over the patient's best-corrected distance prescription while the patient views his or her smartphone or tablet.

He asks the patient, "How does it look? How does it feel? What do you notice?"

Many patients immediately experience sharper vision and greater comfort. After about 15 seconds, Dr. Gosling lifts the flipper. If a patient reacts by pushing the device further from his or her eyes and squinting, then Dr. Gosling knows that he has identified a candidate for anti-eyestrain lenses.

If patients do not have a smartphone or tablet with them, then use your near-point card. A card is a good target, but not as authentic as a backlit digital device.

AN ADDITIONAL TEST

When a patient's behavior indicates benefit from low-add power, Dr. Gosling does one additional test. He repeats the use of the flipper while the patient continues viewing the near tool. He instructs the patient to shift his or her eyes to the distance eye chart as soon as the flipper is raised. If the patient reports comfort at near and clarity at far, again, this is a good candidate for anti-eyestrain lenses.

VENDOR OPTIONS

Before choosing a vendor of choice, study all of the options. A variety of technologies exist, including prism to aid convergence, tints to improve contrast and adjust color spectrum from computer backlights, filters to decrease high-energy visible (HEV) light, and wraps to decrease tear evaporation, plus an assortment of low-add powers strategically positioned in down gaze (Figure 1 on Page 23).

MARKET FORCES

When investigating wholesale price point and vision plan reimbursement, or lack of reimbursement, ECPs might find a wide variance among vendors. This occurs because vendors face a big challenge. The low-add lenses are similar to progressive lenses. Plus-power provides accommodative relief in down gaze, and each brand has a minimum fitting height. However, the target market is young, active, tech-savvy people. These patients do not want the stigma of bifocals—or the expense.

THE ATORIC OPTION

Successful vendors will differentiate anti-eyestrain lenses from single-vision options without claiming progressive lens status. One strategy is to define a lens technology continuum and expand the category of atoric lenses (Figure 2 on Page 23).

This method of differentiation can work. However, those who understand optics might quibble. Realize that in Latin, aspheric means *not sphere shaped*, and in practice aspheric lenses are symmetric around the optical center (OC). Atoric lenses are simply another kind of aspheric shape with topography that is not symmetric around the OC. Using this logic, progressives can be defined as a kind of atoric, such that lens topography becomes increasingly asymmetric in down gaze.

Furthermore, digital manufacturing is similar for all the lenses. Inside robotics-enabled labs, the real difference boils down

Patient New Media Use Questionnaire

SECTION I.

Smartphone	Y/N
Tablet (iPad or Android)	Y/N
e-Reader (Kindle, Nook)	Y/N

How many hours a night do you sleep on average?_____

Please note the number of hours per day spent viewing the following devices:

Smartphone	Tablet	e-Reader
<1hr	<1hr	<1hr
2-4hrs	2-4hrs	2-4hrs
4-6hrs	4-6hrs	4-6hrs
6-8hrs	6-8hrs	6-8hrs
8-10hrs	8-10hrs	8-10hrs
>10hrs	>10hrs	>10hrs

How many hours are you spending viewing a computer?_____

[Typical distance is 18-36 inches.]

SECTION II.

Do you alternate focus between distances? If so, what do you alternate between?

TV & Smartphone?_____

TV & Tablet? _____

TV & e-Reader? _____

Computer & Smartphone? _____

Computer & Tablet?_____

Hobbies? _____

SECTION III.

Do you experience any of the following conditions?

Fluctuation in Vision	Y/N
Tired Eyes	Y/N
Headaches	Y/N
Overall Body Fatigue	Y/N
Decreased Concentration	Y/N
Decreased Night Vision	Y/N
Dry Eyes	Y/N
Light Sensitivity	Y/N
Rubbing of Eyes	Y/N

Figure 1: Anti-Eyestrain Vendor Options

BRAND	LENS	ADD	MIN FIT	WEBSITE (ACCESSED JULY 1, 2013)
Essilor	Anti-Fatigue	0.60 D	13 mm	http://www.essilorvisualfatiguesolutions.com/downloads/LESS200268_AF_Spec_Sheet.zip
Hoya	Sync 5	0.55 D	11 mm	thehoyafreeformcompany.com
Hoya	Sync 8	0.88 D	11 mm	thehoyafreeformcompany.com
Shamir	Relax	0.65 D	16 mm	http://www.shamirlens.com/index.php?option=com_k2&view=item&id=710:shamir-relax%E2%84%A2&Itemid=253
Zeiss	Gunnar	NA	NA	http://vision.zeiss.com/eye-care-professionals/en_us/products-and-technologies/lenses/office-computer-lenses.html

Figure 2: Lens Technology Continuum

to sophistication of proprietary software that calculates the topography for each branded lens design.

Because differentiation is complicated, and market forces are at work, you are likely to discover inconsistencies in wholesale price point and vision plan reimbursement. With this understanding, thoroughly research all vendor options when selecting the anti-eyestrain lens best for your patients and business.

QUALIFIED CANDIDATES

After selecting the anti-eyestrain lens or lenses of choice, match the patient to the product using methods shown above. Then boost your success rate by evaluating every non-adapt. Review their Media Use Questionnaires and symptoms.

Confirm documented acceptance of add-power during show and tell with a plus-lens flipper. Finally, interview to determine the reason for non-adapt. Did the patient experience improved comfort and mental focus? *What happened?*

SUCCESS, ONE PATIENT AT A TIME

Dr. Gosling reports a 95% success rate in identifying patients who will love anti-eyestrain lenses. From his experience, 5% will non-adapt, and the most common reason is what might be predicted. Even a subtle amount of plus-power, positioned in down gaze, alters peripheral vision. Some patients, especially athletes, prefer the edge-to-edge clarity of single-vision, free-form lenses. Dr. Gosling is still learning from case-by-case evaluation of every non-adapt.

DIFFERENTIATE YOUR BUSINESS

Digital devices have revolutionized daily human experience. Today, patients can send text messages, check e-mail, play games, surf the Web, network through social media, enjoy videos, and use multiple digital tools simultaneously. To date, however, there is no app to prevent eye fatigue.

ECPs can make a difference. Embrace new technology lenses. With some research and planning, ECPs can develop business strategies as better and better lens products come to market. Achieve success by helping patients and differentiating your business. ■

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Dr. Jacobs is director of Practice Management Depot. She lectures frequently on practice management topics.

Vision Council combats digital eyestrain

THE VISION COUNCIL raised awareness of digital eyestrain among those audiences most at risk at the 2013 International Consumer Electronics Show (CES). The Vision Council was on hand to help digital-device users protect their eyes from digital eyestrain, a growing health concern for avid electronic consumers.

A 2012 survey by The Vision Council found that nearly 70% of U.S. adults experience some form of digital eyestrain while using digital devices. The majority of Americans spend 4 to 6 hours daily in front of electronics—a number steadily on the rise among younger populations. Individuals can easily protect vision, however, through the use of the wide array of computer eyewear products available today.

"Technology is taking us to fascinating places, and CES is an opportune time to see what innovation will look like [this year]," said Ed Greene, chief executive officer of The Vision Council. "As the largest tradeshow of consumer electronics, CES [provided] us a platform to reinforce safe eye behavior among those adults and children who most frequently use consumer electronics. We are especially excited to [offer] computer eyewear and other eyewear solutions that can help to prevent the risk of digital eyestrain."

What's your pricing strategy?

Explore the variables associated with lowest price or value received for the dispensary

Dispensing Solutions By Arthur De Gennaro

IN THE OPTICAL dispensaries of many ophthalmology practices, there exists a problem: deciding the pricing strategy.

If you ask the average optician, he or she will say that customers are focused on price. In other words, price is what sells eyeglasses. The optician will attempt to set the everyday retail prices of frames, lenses, and lens accessories as low as possible. In his or her opinion, this is the easiest way to get customers to say "yes."

This strategy poses a number of problems:

LOWEST-PRICE CLAIMS.

Watch, read, or listen to most merchants' advertisements and you would think that they all offer the lowest price. Since only one competitor in any given market can have the lowest price on an item, consumers will conclude that most of those competitors are less than truthful. Guaranteeing the lowest price is obviously not a good way to position your dispensary's brand. It does not instill confidence in gun-shy consumers who know from experience that you get what you pay for.

LACK OF SERVICE.

When customers walk into a big-box retail store today, they will have two complaints: they cannot find someone to help them, and when they do find someone, the salesperson is not knowledgeable. This deliberate lack of service is how many retailers are staffing their stores these days. This staffing model is designed to lower prices, and unfortunately, it is also lowering service. Consumers often become angry or frustrated when attempting to make a purchase. In addition, consumers who do make a purchase are less likely to be convinced they made the right decision or purchased from the right company.

CHEAP GOODS.

Another way to keep prices down and margins up is to offer lower-quality goods. That type of merchandise, however, is not designed or manufactured to provide the length of service or type of service for which many consumers are looking. Consumers will be disappointed with their purchase and generally with the retailer that sold it.

PROFITS.

Companies that specialize in offering low prices must earn a profit by selling a lot of items. Selling a lot of items makes up for the lack of profit from each item. Since dispensaries in ophthalmology practices do not sell a lot of pairs of glasses each day, a low-price strategy will only cause the practice not to earn enough profit to make the enterprise worthwhile.

FAIR PRICE FOR VALUE RECEIVED

When marketing, keep in mind that consumers are exposed to the ads of a lot of retailers who are less than truthful. They are also exposed to the lack of service and cheap goods of those merchants. You get to choose your own path, however. The pricing strategy I like is known as fair price for value received. The challenge of adopting such a strategy is to define convincingly what the value received will be for the consumer.

A value strategy should include at least:

CUSTOMER SERVICE.

The value to a consumer of superior customer service seems to be unknown to many retail CEOs. It is my experience as a consultant that superior customer service allows dispensaries to increase prices. Dispensary customers respond to knowledgeable service delivered by opticians who not only offer what they want, but who also have learned to anticipate their needs. This type of service does not happen by accident. It is only available when a practice makes the decision to hire the right people, train them sufficiently, supervise them effectively, and pay them the types of wages that keep top talent.

SELLING BENEFITS.

Customers do not buy products; they buy the benefits of owning those products. The single most effective way to establish the value of a product is to explain truthfully what benefits the customer will obtain from purchasing it. To do this effectively, an optician needs to have a lot of product knowledge. That knowledge will allow the optician to educate the patient. When the patient feels the benefits are worth the price quoted, he or she will make the purchase.

QUALITY.

Opticians will work hard to assure that the products they dispense are made to exacting quality standards. They are so comfortable with the quality that they have forgotten that focusing a patient's awareness on the quality of the product he or she will receive has a lot to do with establishing its value. Consequently, a robust quality assurance program that is also marketed to patients will build consumer confidence in the dispensary, the optician, and the practice overall. When a good quality assurance program is in place and communicated to patients, warranties then become effective value-added marketing tools.

EXCLUSIVITY.

Having one or more lines of products only available in your dispensary will also add value. Focusing the same brands as national chains will only encourage patients to compare prices. Finding exclusive products can be a challenge. Digitally produced progressive lenses are now available from some laboratories that will encourage you to develop your own brand name for them. Such progressive lenses can be priced below the brand-named lenses. This will make them a good value while protecting your margins.

So, I ask, what is your pricing strategy? ■

OT What pricing strategy do you use? Visit **OphthalmologyTimes.com/pricestrategy** to let us know.

My dispensary's pricing strategy is:

- ❍ Price sells eyeglasses
- ❍ Fair and square pricing
- ❍ Good value for price paid
- ❍ Luxury products are worth the price

ARTHUR DE GENNARO *is president of Arthur De Gennaro & Associates LLC, an ophthalmic practice management firm that specializes in optical dispensary issues. De Gennaro is the author of the book The Dispensing Ophthalmologist. He can be reached at 803/359-7887, arthur@adegennaro.com, or through the company's Web site, www.adegennaro.com. He maintains a blog at www.adgablog.wordpress.com.*

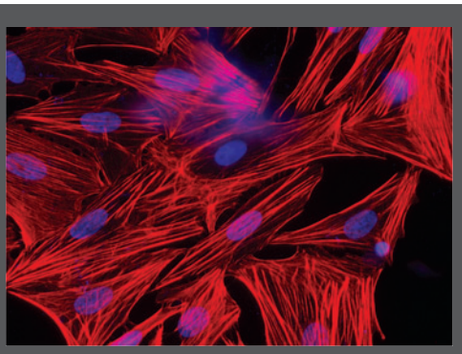
The value of human ocular tissue in eye research

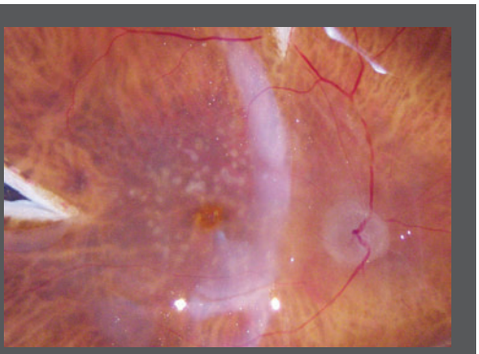
Lessons from ocular tissue research changing understanding of ophthalmic disease

Eye on Research *By Abbot F. Clark, PhD, FARVO*

TAKE-HOME

- ***Human ocular tissue has a critical role in helping researchers understand and find new treatments for diseases that include glaucoma, age-related macular degeneration, and cataract.***





(Figure 1, left) Cultured human trabecular meshwork cells. *(Figure courtesy of Abbot F. Clark, PhD, FARVO)*
(Figure 2, right) All donor eyes obtained by the University of Iowa Institute for Vision Research are prepared in a standard fashion. Gross photographs are obtained, as here. Some of the tissue is preserved in formaldehyde for histology and imaging, while other portions are frozen for future biochemistry studies. *(Figure courtesy of Robert F. Mullins, PhD)*

Most people think of donor eyes in the context of corneal transplantation—as well they should, given the tremendous success of transplantation in saving vision.

However, in the research community, there is an increasing recognition that ocular tissue also has a critical role to play in helping us understand and find new treatments for diseases, such as glaucoma, age-related macular degeneration (AMD), cataract, and more.

GLAUCOMA

In my laboratory, we have used donor tissue from the Lions Eye Institute for Transplant and Research (LEITR) to identify molecular and cellular pathways implicated in glaucoma pathogenesis.

For example, we have been able to culture cells from human trabecular meshwork (Figure 1) and optic nerve head tissue to compare cells from normal eyes with those with glaucoma. We hope to do the same in the near future with retinal ganglion cells.

Other studies have been conducted with an organ culture model in which the anterior chamber is mounted and cultured for weeks. This has helped validate some of the signaling pathways initially identified in cultured cells, and given us a better understanding of the molecular mechanisms regulating IOP in the anterior chamber.

We have also been very successful in harvesting ribonucleic acid (RNA) from both cultured cells and the actual donor eye tissue to compare gene expression in normal versus glaucomatous eyes.

Ongoing research using all of these techniques continues to move us forward, closer to the ultimate goal of understanding what occurs early in the disease process of glaucoma, before there is irrevocable damage and vision loss.

MACULAR DEGENERATION

There is exciting progress on AMD, as well. New techniques have dramatically altered what can be learned from a single tissue sample, said Robert F. Mullins, PhD, associate professor at the University of Iowa, Iowa City, and a faculty member at the university's Institute for Vision Research.

"Ten years ago, studying a single gene might have been a master's degree project," he said. "But with today's RNA analysis methods, we're able to study the expression of 25,000 genes at once if we have high-quality, fresh tissue."

Dr. Mullins' team, working with the Iowa Lions Eye Bank, has imaged and genotyped more than 1,200 donor eyes in the past 8 years (Figure 2). Collecting research tissue on this scale is a huge undertaking and not something most eye banks or universities have made a commitment to, but he believes it is worth the effort.

"Although most human genes have a mouse ortholog, or equivalent gene, one exception is the *ARMS2* gene, one of the major risk factors for AMD," Dr. Mullins said. "We are studying how this and other genetic polymorphisms that increase the risk for AMD affect the biochemistry of the eyes and how the expression of these genes in low-risk, high-risk, and diseased donor eyes differs."

One lesson learned from Dr. Mullins' tissue studies validates optical coherence tomography research that suggests choroidal abnormalities may precede RPE loss in early AMD.

"In the donor eyes with early AMD, there is a clear loss of choriocapillaris endothelial cells," he said. "What that tells me is that the targets for future stem cell therapy interventions may actually be the choroidal vascular cells, rather than RPE cells.

"Further insights into what really causes AMD and how we might intervene are going to come from this kind of work on human ocular tissue," Dr. Mullins said.

Continues on page 26 : ***Ocular tissue***

OCULAR TISUE

(Continued from page 25)

CATARACT

In the field of lens research, scientists at Washington University in St. Louis, St. Louis, MO, are finding that studying vitreous degeneration in eye bank eyes has given them new insights into cataract formation.

"We tend to think of the vitreous as rather uninteresting, but it turns out that the degree of vitreous liquefaction is a better predictor of nuclear opacity than is age," said David C. Beebe, PhD, professor of ophthalmology and cell biology at the university.

Dr. Beebe and his colleagues are working on compounds that could preserve and restore the structure of the vitreous body, as well as compounds that could be added to the lens to reverse age-related changes.

Here again, human tissue fills a critical need.

"The protein changes that slowly increase the stiffness of the human lens nucleus, contributing to presbyopia and cataracts, aren't well reflected in any animal model," Dr. Beebe said. Unfortunately, he said, most basic scientists engaged in lens research have never even seen a human cataractous lens—something Dr. Beebe wants to change.

"In the mouse lenses we typically work with, cortical cataracts occur right on the surface of the lens," Dr. Beebe said. "The first time I dissected a human lens with a cortical cataract, I immediately appreciated how different it was–the cataracts are deeper in the cortex, at the interface between hard nuclear cells and soft, healthy cortex," he recalls.

"That completely changed my perspective on the role of physical damage to lens fiber cells in cortical cataract development," he said.

ANTERIOR SEGMENT SURGERY

Although cataract and refractive surgeons might not think of their bread-and-butter procedures as being based on donor eye studies, it would be impossible to perform these procedures without irrigating solutions, viscoelastics, and topical antibiotics—all of which have been extensively studied in human eye bank eyes.

"To determine that phacoemulsification could be tolerated by a 70- or 80-year-old human corneal endothelium, we had to test it in human tissue," said Henry F. Edelhauser, PhD, professor of ophthalmology, Emory University, Atlanta.

Today, the safety of phaco is well established, but tissue studies continue to be valuable in evaluating new femtosecond laser technology.

Drug delivery is another area of interest for Dr. Edelhauser.

"Certainly for any topical medication, the cornea plays an important role," he said. "We want to know how well the drug penetrates the cornea, where it accumulates, and whether it is toxic."

Although the initial screening of drug candidates and formulations can be done in animal eyes or other laboratory models, testing must be replicated in donor eyes to ensure a similar rate of diffusion through the human cornea.

> 'Human ocular tissue will be the driving force for drug discovery and pre-clinical research models.'
>
> — Jason K. Woody, president and chief executive officer of LEITR

Dr. Edelhauser's current research focuses on delivery methods that bypass the cornea altogether. Using donor eyes from LEITR, he and his team are using a microneedle to inject into the suprachoroidal space (between the sclera and choroid) to see how various agents spread to the retina. This technology could potentially make injection of anti-vascular endothelial growth factor agents, for example, safer and more efficient. Innovative new microbeads and nanoparticles for a range of sustained-release therapeutic applications are also being tested in human tissue.

"The FDA is already moving away from animal-only studies," said Jason K. Woody, president and chief executive officer of LEITR. "We believe that human ocular tissue will be the driving force for drug discovery and pre-clinical research models in the future."

MEETING THE NEED

From this sampling of research endeavors, the value of ocular tissue in advancing scientific knowledge of ocular diseases is clear. The United States has a very strong network of eye banks and a cultural climate that supports the use of donor tissue for research. Nevertheless, there remain many challenges.

Organ and tissue donation rates, especially among ethnic groups that are disproportionately affected by ocular disease, are lower than desired. Few eye banks have dedicated resources to obtain and characterize research tissue. And many researchers do not even consider ocular tissue in designing their experiments. Finally, changes in donor eye procurement and broadening of eligibility for transplant have, to some degree, made it more challenging for researchers to obtain the tissue needed for scientific studies.

Organizations like LEITR that emphasize both transplantation and research help to bridge the gap and highlight the importance of such research. In the future, it is hoped that there will be an even greater awareness of how clinicians and scientists can collaborate to make the best use of the great gift of ocular tissue. ■

About this series

EYE ON RESEARCH is a quarterly series of articles highlighting cutting-edge ophthalmic research with the potential to have a significant effect on vision and ocular health worldwide. The series is supported by the Lions Eye Institute for Transplant and Research Inc. (LEITR), a nonprofit organization dedicated to the recovery, evaluation, and distribution of eye tissue for transplantation, research, and education. Located in Tampa, FL, LEITR is the only combined eye bank and ocular research center in the world. LEITR provides fresh donor globes, corneas, lenses, trabecular meshwork, and other tissues from diseased and healthy human eyes, often within 4 to 6 hours of death, to researchers for immediate use in their own labs or in its onsite research facility. For more information, contact *info@LionsEyeInstitute.org* or visit *LionsEyeInstitute.org*.

What role(s) do you foresee for human ocular tissue in research? Weigh in at **Facebook.com/OphthalmologyTimes**.

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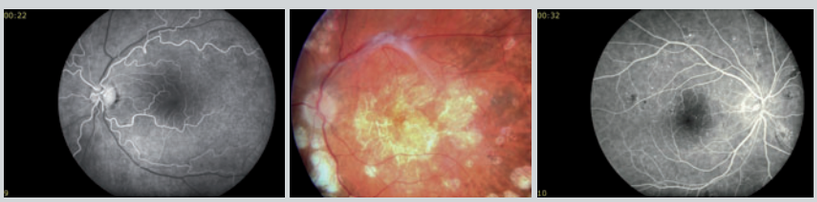

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Vitreous history in the making

Much has changed since the early days of vitrectomy, as exemplified in texts

Our Ophthalmic Heritage *By Norman B. Medow, MD, FACS*

NO MENTION OF vitreous surgery is found in the 1892 edition of "Diseases of the Eye," by G.E. deSchweinitz, MD, then professor of ophthalmology at the University of Pennsylvania, Philadelphia. In the 1910 edition of the book, by John Elmer Weeks, MD, professor of ophthalmology at New York University, Dr. Weeks comments on vitreous surgery in two situations:

- **If vitreous is encountered during a cataract operation, it may be excised if only to allow the lips of the wound to be approximated.**
- **If vitreous opacity is dense and immobile, it may be incised.**

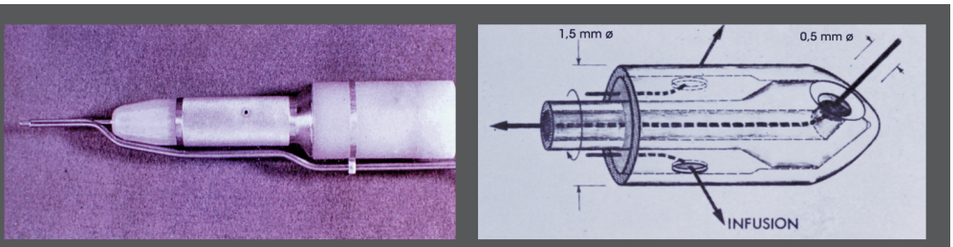
Fast forward: In 1968, David Kasner, MD, an ophthalmologist at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, and a respected teacher of cataract surgery, excised the vitreous in a case of primary amyloidosis.[1] In this open-sky technique, he also showed that vitreous excision postcataract surgery was well tolerated by the eye. This technique was fraught with potential complications: expulsive hemorrhages and iris and corneal damages, as well as needing to render the patient aphakic by removing the lens.

With this in mind, Robert Machemer, MD (1933–2009), was then doing research to develop a closed system for operating on the vitreous body. The technique became known as pars plana vitrectomy. Dr. Machemer and associates, Edward Norton, MD, and Thomas Aaberg, MD, would report on their early experiences with vitrectomies in 1969 and 1970. Most of these patients had vitreous hemorrhages. Later, they would operate on patients with proliferative diabetes.

In 1979, Dr. Machemer and Dr. Aaberg from Wisconsin co-authored a book on vitreous surgery. The same year this book was published, Dr. Machemer moved to Duke University, Durham, NC, where he became chairman of the ophthalmology department.

HOW TIMES HAVE CHANGED

Much has changed since these early days of vitreous surgery. The vitreous infusion suction cutter (VISC) was the name of the original instrument that Dr. Machemer developed (Figure 1). Irrigation, aspiration, and cutting all were done within this single-port, 19-gauge instrument.



(Figure 1) The vitreous infusion suction cutter (VISC) was the name of the original instrument that Robert Machemer, MD, developed. Irrigation, aspiration, and cutting all were done within this single-port, 19-gauge instrument. *(Photos courtesy of Norman B. Medow, MD, FACS)*

Now, vitrectomies are performed using a three-port, 23- and/or 25-gauge system. The earliest vitrectomies were used for vitreous hemorrhage, whereas now vitrectomies are coupled with membranectomy, retinotomy, and retinectomy—all of which are coupled with either the use of silicon oil replacements or heavy gases to aid in securing the retina in place postoperatively.

Only time will tell what advances over the next 20 years will aid vitrectomy specialists with this surgery and with fewer complications. ■

Reference

1. Kasner D, Miller GR, Taylor WH, Sever RJ, Norton EW. Surgical treatment of amyloidosis of the vitreous. *Trans Am Acad Ophthalmol Otolaryngol.* 1968;72:410-418.

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