August 15, 2013
VOL. 38, NO. 16

Ophthalmology Times®
CLINICAL NEWS & ANALYSIS

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PLUS+ FEMTOSECOND LASER : STANDARD OF CARE?

SPECIAL REPORT
OCULAR ALLERGY
TIPS AND THERAPIES

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Glaucoma

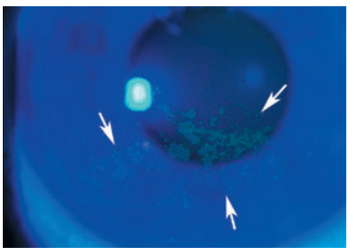
CATARACT SURGERY NOW CAN HELP GLAUCOMA LATER

STANFORD, CA :: **A TREATMENT OPPORTUNITY** exists to lower IOP by an average of 3 to 4 mm Hg for at least 3 years. But this treatment is not a drug, it is clear corneal phacoemulsification. The treatment is generally safe, cost-

(See story on page 17 : Early)

General

WHY MANAGING DRY EYE AIDS LASER VISION CORRECTION

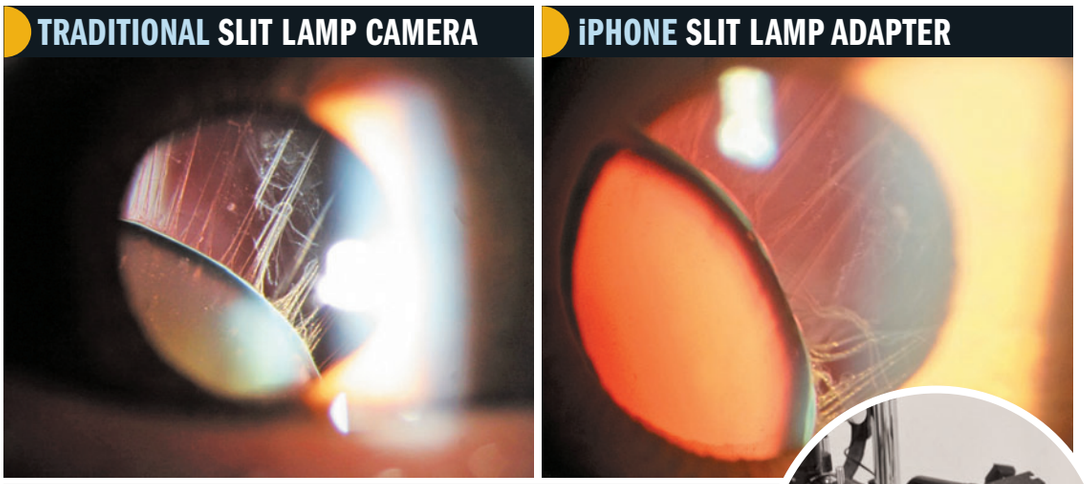


CLEVELAND :: **IDENTIFICATION AND** management of dry eye is crucial for achieving successful outcomes and patient satisfaction after laser vision correction, said Steven E. Wilson, MD. "When it comes to dry eye after LASIK, prevention through preoperative man-

(See story on page 8 : Dry eye)

iPhone *may replace* slit lamp photos

How image quality can be potentially better than conventional photographs, more cost effective



IN VIEW: A subluxed lens, as captured through a traditional slit lamp camera and an iPhone slit lamp adapter. *(Images courtesy of George Magrath, MD, MBA)*

By Fred Gebhart
Reviewed by George Magrath, MD, MBA

CHARLESTON, SC
RECENT iPHONES CAN be used in place of traditional slit lamp cameras with image quality similar to conventional photographs.

"We started using the iPhone to be able to take pictures 24 hours a day, 7 days a week," said George Magrath, MD, MBA, Storm Eye Institute, Medical University of South Carolina (MUSC), Charleston, SC. "[In the past], a lot of ocular pathology [might have] come in over the weekend or overnight, [when] we were unable to use our slit lamp camera because the department was closed, the technician wasn't available, or we were in the emergency room.

"Being able to use a phone camera is a tremendous boost to clinical practice," he said.

A slit lamp camera, in trained hands, can produce clear, high-resolution images of the anterior segment. But such cameras can cost up to $10,000 and require the services of a trained slit lamp photographer to produce consistent, high-quality results.

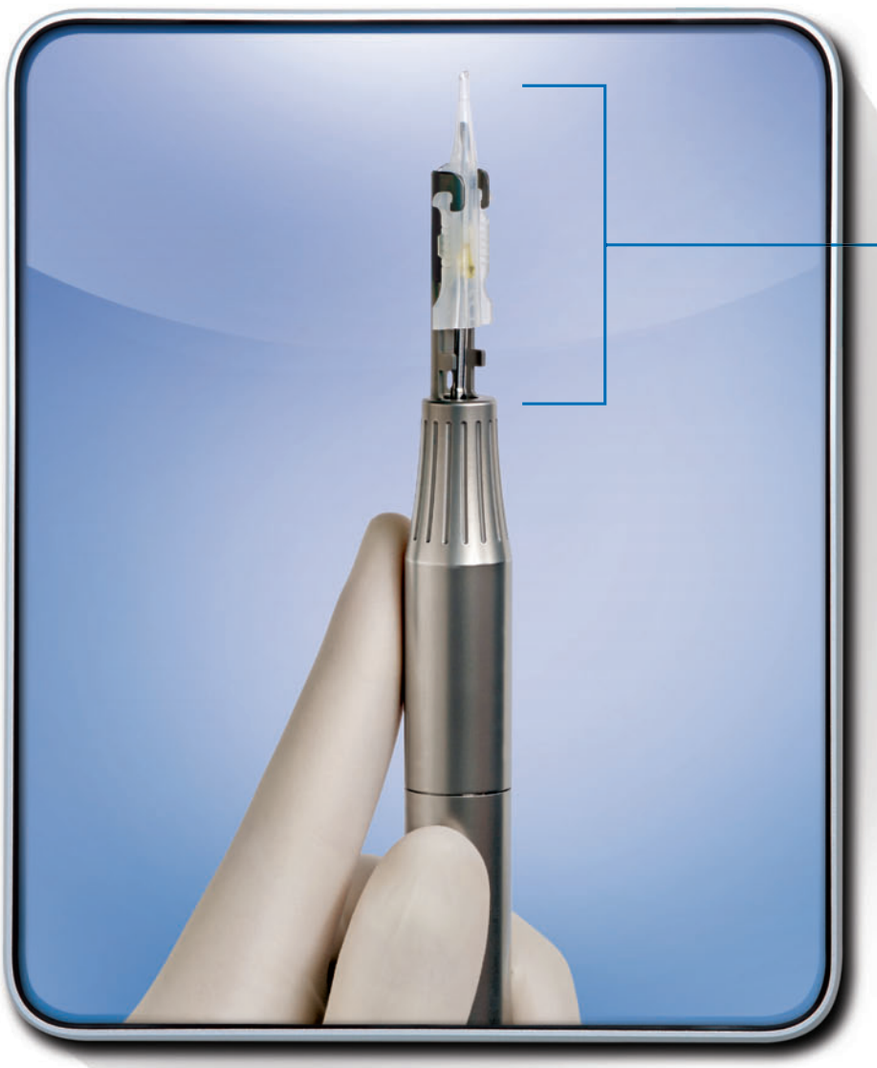
(Continues on page 9 : Images)

DO YOU PREFER

MORE CONTROL

— OR —

MORE CONSISTENCY?



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1. Johansson, C. Comparison of Motorized IOL Insertion to Traditional Manual IOL Delivery. ASCRS Presentation, 2011.
2. Allen, D. Experience with Electro-Assisted IOL Injection Device. ASCRS Presentation, 2011.

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General

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Focusing on dry eye before surgery leads to better postop results, happier patients

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ECPs have a duty to warn patients of the safest and best lens material

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Words of wisdom

Advice from the 13th century rings true for today's ophthalmologists

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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JOHN OF GARLAND, writing some 900 years ago, provided excellent advice to the young persons of his time—advice that we ophthalmologists today would be wise to heed. He begins with the importance of good nutrition and moderation in eating and drinking:

"Polite diners pause over their cup, but gluttons, who live like mules and weevils (sic), empty it with one draught. Always serve two pieces of bread. He who takes a walk or a brief nap after dinner preserves his health. If you wish to regain your strength as a convalescent, and keep your health when you are well, drink moderately. All Epicureans live impure lives; they lose their eyesight; they are rude, unclean and are doomed to die a sudden death . . . "

The observation that excessive eating will specifically cause blindness, made so long ago, is an interesting one. It is the only specific medical problem mentioned by the author, who was a philologist and university professor (not a physician). John of Garland was probably born around 1190 and taught at the University of Toulouse in 1229.

MERITS OF GOOD DIET AND EXERCISE

Apparently, John of Garland had never studied medicine, but nonetheless seemed to appreciate the relationship between gluttony and visual loss, presumably the result of obesity-related diabetes mellitus, centuries before that disease was "discovered."

Unfortunately, despite at least 1,000 years of warnings about overeating, we humans still fail to take this advice to heart. Fortunately (for him) John of Garland did not live to observe my glutinous behavior in the restaurants of "The Big Easy," whose Cajun cuisine I have never been able to enjoy in moderation.

Sadly, it seems to me, educating people about the health benefits of a good diet and the dangers of overeating has failed to keep our species from suffering an epidemic of obesity. Some political leaders, like New York's Mayor Michael Bloomberg, believe the solution lies in laws limiting the sizes of servings. His efforts to ban the "Big Gulp" in New York were derided by some as a nanny-state tactic, before being ultimately blocked by the courts.

The recommendation of a walk after dinner is one that makes good sense to me, and I know many people who make a habit of this.

Why John of Garland believed that a postprandial nap is just as good as a walk is a mystery to me. He goes on to say: "When you walk after dinner keep on frequented streets." When walking at night in unfamiliar cities, such as when attending ophthalmology meetings, ophthalmologists should probably take this advice.

MONEY MATTERS

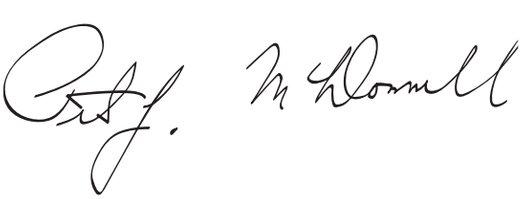
On financial matters, this advisor from medieval times does not subscribe to the "neither-a-borrower-nor-a-lender-be" school of thought.

Rather, said John of G: "Hasten to help a needy friend, give him money if you can. Be a good debtor and hasten to pay your debts lest you be condemned by your burden of sin and by the peasant bewailing his losses."

I am also pretty sure John of Garland had ophthalmology meetings in mind with his next bits of wisdom: "Avoid insincere speeches. Unless you wish to be considered a fool, learn to keep your mouth shut in season."

Finally, offers John: "Stand and sit upright, do not scratch yourself."

Words to live by. ■



Reference

- How the student should behave. John of Garland. In: The Medieval Reader. Viking Press, New York, 1949.

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Ophthalmology Times is a physician-driven publication that disseminates news and information of a clinical, socioeconomic, and political nature in a timely and accurate manner for members of the ophthalmic community.

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.

ACA provision offers no 'grace' to practices

By Donna Marbury, MS

WASHINGTON, DC ::

Starting in January, practices will have the extra burden of collecting on denied claims from patients due to a 90-day grace period provision of the Affordable Care Act (ACA).

The Medical Group Management Association (MGMA) says this grace period makes practices more like collection agencies. The association also offers a solution: insurers must notify practices that a patient has entered the grace period during eligibility verification requests.

Here's how it works: insurers must give patients in exchanges 90 days to pay premiums. Insurers will pay any claims made in the first 30 days, and will hold claims in the past 60 days. If the patients haven't paid premiums for services in the past 60 days, they can be dropped from their plans and must pay the practice full price.

This provision is supposed to help patients who are not used to being in the health-care system with more time to make payments. The problem is, some patients are unaware of the stipulation, and could end up owing practices a great deal of money.

"If patients don't realize they are in the grace period, they will be financially responsible for a bill much bigger than it needs to be," said Allison Brennan, senior advocacy adviser for MGMA. "Practices are in business to provide care and don't want to be focused on collecting debt."

STARTING IN JANUARY, PRACTICES WILL HAVE THE EXTRA BURDEN OF COLLECTING ON DENIED CLAIMS FROM PATIENTS DUE TO A 90-DAY GRACE PERIOD PROVISION OF THE ACA.

On July 3, MGMA President Susan Turney, MD, wrote a to the U.S. Department of Health and Human Services (HHS), decrying the 90-day grace period, and calling for insurance companies to provide real-time eligibility verification to practices.

Continues on page 7 : **Grace period**

HEADLINES YOU MIGHT HAVE MISSED

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

SLEEP APNEA, GLAUCOMA LINK?

PATIENTS WITH SLEEP APNEA ARE MORE likely to develop glaucoma compared with those without the sleep condition. A study found that the risk of developing open-angle glaucoma within 5 years of an obstructive sleep apnea diagnosis was 1.67 times higher in those who had sleep apnea compared with control.
http://bit.ly/16bKyDJ

JSEI, DOHENY SEEK LONG-TERM ALLIANCE

THE UNIVERSITY OF CALIFORNIA, LOS ANGELES' Jules Stein Eye Institute (JSEI) announced it is pursuing a long-term affiliation with the Doheny Eye Institute. The proposed affiliation would preserve each organization's identity and mission, and align strengths that have factored into advancing ophthalmology through research, outreach, education, and patient care.
http://bit.ly/18vd0Rk

FDA GIVES NOD FOR OAG PHASE I TRIAL

INNFOCUS HAS RECEIVED AUTHORIZATION from the FDA to begin the phase I trial with the InnFocus MicroShunt to treat open-angle glaucoma (OAG).
http://bit.ly/1cNU2u9

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Recent hashtags *Ophthalmology Times* has used on **twitter.com/OphthTimes**

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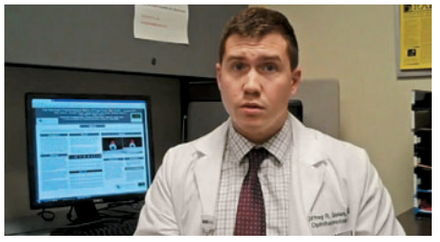
Video

Jeffrey R. Golen, MD, says pupils can be pharmacologically dilated after death. Go to *http://bit.ly/11031Sm*



In Brief

FROM STAFF REPORTS

Expands vision portfolio

ABBOTT COMPLETES ACQUISITION OF OPTIMEDICA

ABBOTT PARK, IL ::**ABBOTT HAS COMPLETED** its acquisition of OptiMedica for $250 million.The acquisition expands Abbott's vision-care business into the femtosecond laser-assisted cataract surgery market by way of OptiMedica's Catalys Precision Laser System.

The laser system, which is designed to allow surgeons to replace some of the technology demanding manual steps in cataract surgery, has received both CE Mark in Europe and clearance from the FDA.

"OptiMedica's (laser system) enhances Abbott's leadership position in vision care with the addition of a state-of-the-art laser cataract technology to our portfolio," said Murthy Simhambhatla, PhD, senior vice president of medical optics for Abbott. "OptiMedica's technology, combined with Abbott's global market presence, offer the potential to provide advanced cataract treatment options to more patents around the world."

While Abbott paid $250 million to acquire OptiMedica, additional amounts totaling up to $150 million will be payable upon completion of various development, regulatory and sales milestones.

GRACE PERIOD

(Continued from page 6)

The MGMA, which represents 22,500 members who lead 13,200 medical practices or serve as professional administrators, believes that insurers should have to follow the same Health Insurance Portability and Accountability Act (HIPAA) law that requires them to provide patient eligibility information within 20 seconds (or overnight for large requests) to practices.

As of now, insurers are required to tell practices of coverage eligibility within a "practicable" amount of time for exchange patients, according to the Centers for Medicare and Medicaid Services.

Because exchange patients are receiving coverage directly from insurance companies and not from an employer, there should be no wait to know whether their accounts are current. Real-time verification would at least allow practices to inform patients of their status.

This could help patients avoid a costly payment, and practices dodge a cumbersome collection process.

"One of the key things we want to see is that insurers are required to provide information about the grace period when the practice calls, or requests it electronically. It is already common for a practice to do this to make sure the patient has insurance. Our concerns are that insurers won't provide the information," Brennan said.

The MGMA has yet to receive a response from government officials, according to Brennan.

"There has been a lot of focus on ACA implementation, and we are already seeing changes," Brennan said. "We hope the HHS revisits this particular issue because it will ease the fears of practitioners and help patients be more aware of their financial situation."

In the meantime, Brennan suggests that small practices consider aligning with a collection agency to handle what may be an influx of unpaid bills.

"We also encourage practices to do an eligibility verification request on every patient every time they come in for services," she said. ■

Want to weigh in on the debate about the 90-day grace period provision of the ACA? Share your comments on **Facebook.com/OphthalmologyTimes.**

CORRECTION An *Ophthalmology Times* supplement published earlier this year with highlights from the Glaucoma 360° meeting contained two typographical errors. The name of one of the 2013 Catalyst Award winners identified in the photo caption on page 3 should be Paul S. May. Also, Louis Cantor, MD, spoke during the Shaffer-Hetherington-Hoskins Lecture (page 4). *Ophthalmology Times* regrets the errors.

Why managing dry eye crucial in laser vision correction success

Focusing on dry eye prior to surgery leads to better postop results and happier patients

By Cheryl Guttman Krader; *Reviewed by Steven E. Wilson, MD*

TAKE-HOME

- ***Proactive handling of pre-existing dry eye in patients undergoing laser vision correction will improve the accuracy of custom ablations and lower the risk of postoperative dry eye-related problems.***

CLEVELAND ::

Identification and management of dry eye is crucial for achieving successful outcomes and patient satisfaction after laser vision correction (LVC), said Steven E. Wilson, MD.

"When it comes to dry eye after LASIK, prevention through preoperative management is the best treatment," said Dr. Wilson, professor of ophthalmology and director of corneal research, Cole Eye Institute, Cleveland Clinic, Cleveland. "By avoiding postoperative dry eye and LASIK-induced neurotrophic epitheliopathy (LINE), your patients will be much happier and therefore more likely to refer."

Dr. Wilson

Dry eye after LVC is an overlap condition consisting of inflammatory-based dry eye—which may exist prior to surgery—and LINE, which develops postoperatively due to loss of nerve-secreted trophic factors necessary for epithelial cell viability.

Since pre-existing inflammatory dry eye exacerbating after LASIK is a risk factor for more severe LINE—which mostly presents with bothersome fluctuating vision and can compromise the refractive outcome of a custom ablation by confounding the wavefront analysis—surgeons must be proactive in addressing dry eye, Dr. Wilson said.

The need to screen LVC candidates for existing dry eye is reinforced by patients with dry eye experiencing contact lens intolerance and thereby self-select for refractive surgery.

Treatment to normalize the ocular surface prior to surgery is indicated in any patient with punctate staining. Topical cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) is the treatment of choice and is supplemented routinely with non-preserved artificial tears, Dr. Wilson said.

A topical corticosteroid can be added to hasten the response in cases of more severe dry eye.

Other modalities for dry eye management, including punctal plugs, dietary supplements, and attention to environmental factors (e.g., room humidity), may also be part of the management plan.

Patients are re-evaluated after 1 month and those with mild dry eye may have an adequate response and can proceed with surgery.

However, if corneal staining persists and the Schirmer test score is ≤5 mm, patients are instructed to continue with cyclosporine for another few months before re-evaluation.

If the Schirmer test score does not exceed 5 mm, he said, PRK may be cautiously considered as an alternative to LASIK, but many of these patients are not candidates for PRK or LASIK.

Cyclosporine is stopped on the day of LVC and then continued for 6 to 8 months postoperatively.

LINE MANAGEMENT

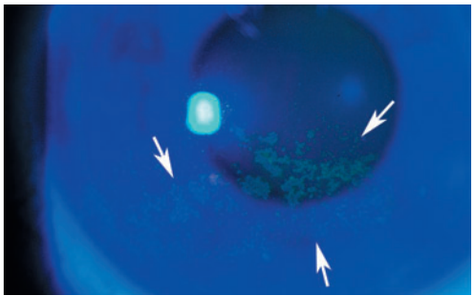
Some patients may develop LINE in the absence of pre-existing dry eye. However, many of those individuals could have had occult inflammatory dry eye predisposing them to LINE.

If LINE develops, topical cyclosporine is again the treatment of choice.

More than 85% of patients will respond within 1 month after starting the immunomodulator, Dr. Wilson said. If patients have good tear production, a bandage contact lens may also be placed for the first few months after surgery to limit vision fluctuation associated with LINE. LINE that does not respond to topical cyclosporine may be expected to resolve spontaneously at 6 to 8 months postoperatively when the nerves regenerate into the flap.

LASIK CHRONIC PAIN SYNDROME

Patients who complain of ongoing pain, despite effective treatment of dry eye and other ocular surface conditions, may have LASIK chronic pain syndrome—a very rare condition that is thought to represent an ocular reflex sympathetic dystrophy.



A cornea (Mag 25 ×) of a patient whose LASIK-induced neurotrophic epitheliopathy developed at 1 week after surgery with no history of dry eye prior to LASIK. *(Image courtesy of Steven E Wilson)*

Dr. Wilson said he first described LASIK chronic pain syndrome in 2008 after making the diagnosis in 2 patients.

Over the next 5 years, he encountered the condition only once.

"Refractive surgeons may see just 1 or 2 patients with LASIK chronic pain syndrome in their careers," Dr. Wilson said.

Pain intensity in patients with LASIK chronic pain syndrome varies from day to day. It appears to respond to gabapentin, pregabalin, or topiramate.

Ophthalmologists unfamiliar with those medications, which are dosed with upward titration, may consider collaborating with a neurologist or other colleague who is accustomed to prescribing them.

All 3 patients he has seen with LASIK chronic pain syndrome, Dr. Wilson said, had a procedure using a mechanical microkeratome for flap creation.

However, with so few cases, it cannot be said whether that technique is a risk factor, he concluded. ■

STEVEN E. WILSON, MD

E: *wilsons4@ccf.org*

Dr. Wilson is a consultant to and serves on the speakers' bureau for Allergan.

IMAGES

(Continued from page 1)

TAKE-HOME

- ***In comparing conventional slit lamp photography with iPhone images, it was found the smartphone produces higher-quality pictures and in a more economical way.***

An iPhone—in the hands of a resident or an emergency room physician—can also produce clear, high-resolution images of the anterior segment. The complete photographic set-up, including iPhone and slit lamp adapter, costs less than $350 and can be used with any slit lamp in any physical location.

DISCOVERING THE TECHNOLOGY

What began as a work-around for first-year residents to send relevant patient images to their back-up or to on-call ophthalmologists is expanding.

Emergency room physicians and providers have a need for immediate images for triage and treatment consults or to store for later teaching use.

The entire photographic system is little more than an iPhone, case, a clamp that holds the phone to the slit lamp ocular, and a base plate that stabilizes the phone on the fellow ocular in landscape mode.

The original adapter was based loosely on an Instructables.com presentation, but the adapter has many enhancements to provide the image quality needed for clinical use.

HOW IPHONE CAPTURES IMAGES

Image capture uses standard iPhone controls.

In addition to simple, intuitive photographic controls and an excellent onboard image capture system, the iPhone offers built-in, high-dynamic range photography.

One setting captures three images in quick succession: one underexposed, one neutral, and one overexposed. The software then produces a final image with improved dynamic range.

The iPhone also offers many lighting techniques. In addition to standard oblique, slit beam, and retro modes, the phone can be used with ambient room lighting to capture images quickly of gross pathology, such as corneal ulcers and defects in the eyelid.

BENEFITS TO PATIENTS

"Patients love the iPhone adapter," Dr. Magrath said. "They see it as a good use of a technology they already know about, even if they don't have a smartphone themselves.

"They like not having to move to another room for photography, which in our institution means walking up stairs," he said. "They appreciate how quick and easy it is and that it is something that can be done then and there. . . . It makes for a less intimidating, less stressful exam. If you're the physician, you known then and there that you have the images you want."

However, using a camera phone to capture patient images could present privacy concerns, Dr. Magrath said.

MUSC physicians obtain informed consent and upload images directly into a patient's electronic medical record, then delete the images from their phones to prevent transmission to a third party either intentionally or accidentally.

All iPhones at MUSC must be password-protected in case the phone is lost.

In other settings, the same system is used to send images to ophthalmologists on-call for advice on triage or immediate treatment.

"That ability to send photos to a remote expert and get immediate feedback is a powerful clinical tool," Dr. Magrath said

LOOKING FORWARD

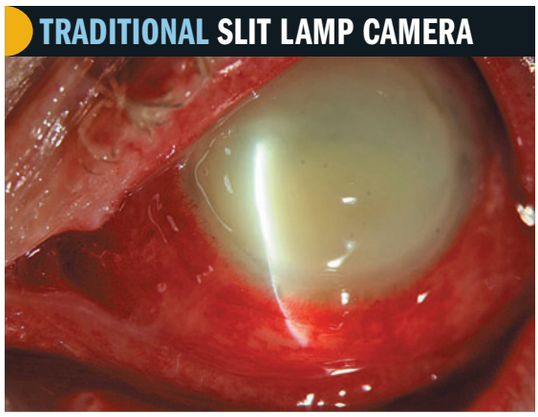
The next step in his clinical research program is an unblinded study where lower-level residents send images to more senior residents for evaluation. Emergency room personnel would send images to the ophthalmology residents for evaluation and recommendations.

Telemedicine findings and recommendations could then be compared with in-person exams.

Another avenue for research is using blinded observers to evaluate image quality and clinical utility of iPhone images versus traditional slit lamp images.

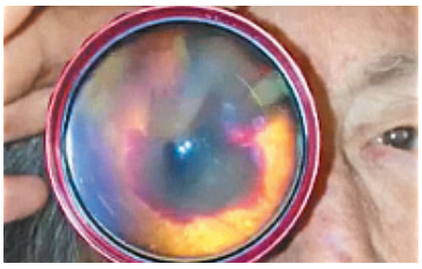
There are also questions about the utility of images from other types of phones.

Dr. Magrath said he has only used the iPhone for slit lamp photography, but does not see any reason why a similar system would not work with an Android or other phone with equivalent image capture capabilities. ■



(FIGURE 1) **Images of *Pseudomonas* ulcer, as captured through a traditional slit lamp camera (top) and an iPhone slit lamp adapter (bottom).**
(Images courtesy of George Magrath, MD, MBA)

APPLICATION IN USE



VIDEO Acute intraretinal hemorrhage from a choroidal neovascular membrane in exudative age-related macular degeneration. Taken using an iPhone 5 and standard camera app with a Volk digital clearfield 20 D lens. Go to **http://youtu.be/3eqM_ODWUEU.** *(Video courtesy of David Tremblay, MD)*

GEORGE MAGRATH, MD, MBA
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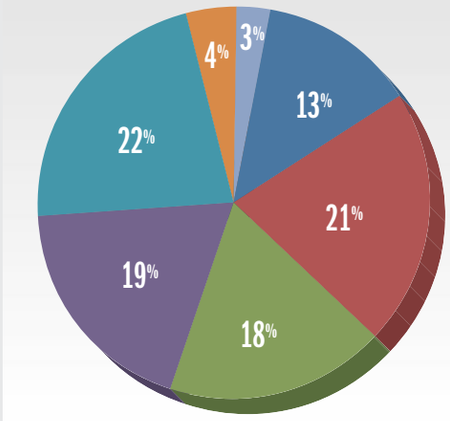
Dr. Magrath has given instructions or constructed iPhone slit lamp adapters for physicians on request, but has no financial interest.

AN UPDATE ON OCULAR ALLERGY TRENDS

By Emily Schoemmell and Paul Gomes; *Special to* Ophthalmology Times

Figure 1: Surveyed Demographics



Graph shows age distribution of the 205 respondents comprising 121 women (59%) and 84 men (41%).

Age

- <18
- 18 to 29
- 30 to 39
- 40 to 49
- 50 to 59
- 60 to 64
- ≥65

take-home

- **Recent data show that although ocular allergies are common, the majority of sufferers do not seek medical help beyond over-the-counter drugs.**

Ocular symptoms of allergic conjunctivitis are common and quite often interfere with quality of life for affected individuals.

There is a paucity of national and international data evaluating the prevalence of ocular allergies within adult populations. As the worldwide population grows, so does interest in gathering and understanding how allergic conjunctivitis sufferers get by daily.

CONCERNS

Existing survey data—including studies from a number of European countries and the United States—suggest a significant overlap in allergy prevalence, and a relatively low (10% to 20%) percentage of patients seeking treatment for their allergies.[1]

In an epidemiologic study on 4,991 first-time patients consulting allergy services in Spain, 55% of patients with allergic rhinitis were diagnosed, of whom 65% also had allergic conjunctivitis.[2]

It has also been well documented that itchy/red eyes or watery eyes is considered to be a most troublesome symptom for patients with allergic rhinitis/conjunctivitis. Recently, an Allergies in America survey found the most common eye complaints in patients with allergic rhinitis were also watery eyes, itchy eyes, and red eyes.[3]

In an international survey on the impact of allergic rhinitis on health-related quality of life, itchy/red eyes were reported by 64% of patients in the United States, with mixed forms of rhinitis and more commonly than in independent forms of seasonal or perennial allergic rhinitis.[4]

In order to stay well-versed in therapeutic strategies and to understand better how ocular allergies are affecting the patient population, continual assessments of the allergic population is of utmost importance.

DIGGING DEEPER

A survey was conducted to assess the demographics of history and treatment prevalence in allergic conjunctivitis sufferers in the Merrimack Valley region of Massachusetts (Figure 1).

The goal of the study was to compare a population of people who suffer from allergic conjunctivitis with national and global averages and to identity potential emerging trends. Subjects who were part of an ocular allergy clinical trial database and who agreed to participate in a clinical trial were asked to participate in the IRB-approved questionnaire.

Of 230 subjects, 205 completed questionnaires were included in the survey analysis.

The population of respondents was generally representative of the total database of trial participants in terms of age, racial distribution, and the relative numbers of men and women. Subjects provided information on disease characteristics, treatment strategies, and satisfaction with their current therapeutic regimes.

The population consisted of 59% women and 41% men, with a mean age of 37.8 years.

The overwhelming majority (83.9%) reported experiencing nasal as well as ocular allergy symptoms, while smaller percentages (18% to 31%) stated they also suffered from food allergies, skin allergies, or asthma. About 1 in 4 reported some type of allergy to medication.

As a group, the respondents reflect recent national trends: 38% experience allergic symptoms year-round, while 62% have allergies confined to one or more seasons (Table 1 on Page 13).

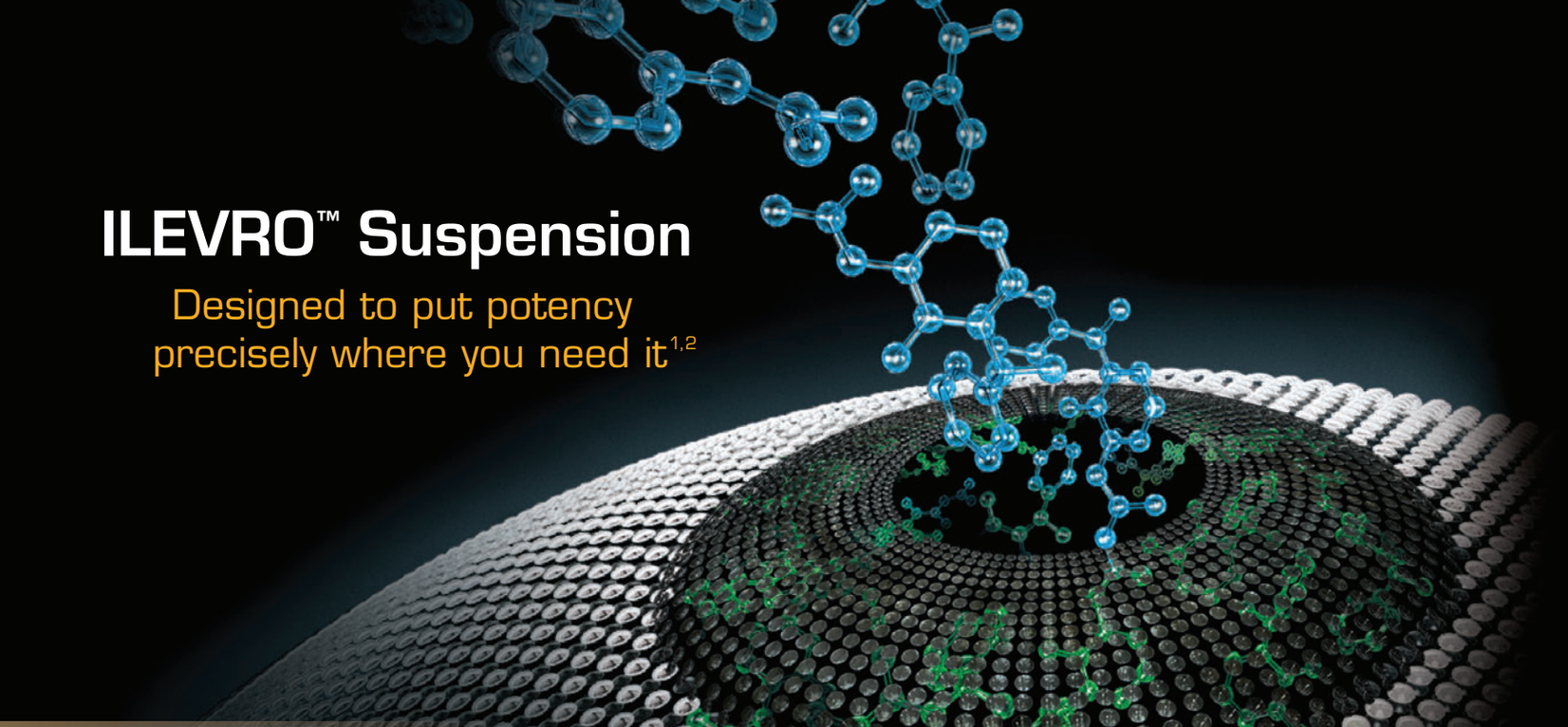
The second-most reported complaint, after ocular itching, was excessive tearing or watery eyes, followed by ocular redness (Table 2 on page 13).

A high percentage of respondents also reported not seeking treatments for allergies (Table 3 on Page 13).

Seventy-one percent of respondents with seasonal allergies and 53% with perennial allergies said that they have not sought treatment from an eye-care professional, and 41% reported that they do not regularly purchase over-the-counter medications to treat their allergies.

Despite this, 89% of respondents that used drops reported that they are effective "all or most" of the time.

Continues on page 13 : ***Trends***



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- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

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

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

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

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

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

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Special Report 〉 **OCULAR ALLERGY**

Tips for tackling conjunctivitis

How one practice uses diagnostic test to manage signs, symptoms in allergy season

By Rajesh K. Rajpal, MD; *Special to* Ophthalmology Times

AS CLINICIANS AT A REFERRAL cornea practice, my colleagues and I treat many patients who present with red eye. During allergy season, when allergic conjunctivitis is more prevalent, it is beneficial to implement a protocol that differentiates among allergic, adenoviral, and bacterial conjunctivitis.

Every member of our staff plays an integral role in executing a red eye protocol for conjunctivitis built around the point-of-care diagnostic test (AdenoPlus, Nicox). When patients present with red eye, they are checked in by the staff at the front desk. The technician escorts the patient from the waiting room to an isolated examination room in an effort to minimize the chances of a potentially infectious patient exposing others in the office.

take-home

- **Utilizing a red eye protocol can be helpful in the determination of whether conjunctivitis is allergic, viral, or bacterial.**

When the technician examines the patient, he or she is careful not to interact in a way that spreads contagion, such as shaking hands. If the technician suspects the patient is contagious, he or she alerts the clinician and obtains permission to proceed with diagnostic testing, prior to applying any drops or using any instruments that may touch the patient's eye.

If the clinician determines that the patient may be infectious, the clinician will instruct the technician to perform the point-of-care diagnostic test to rule out or confirm the presence of adenoviral conjunctivitis. The technician administers the test, waits 10 minutes for results to appear, and informs the clinician of the results. The clinician conducts a full examination on the front surface of the patient's eye to determine that there aren't any other contributing factors to the patient's symptoms.

If the test is negative for adenoviral conjunctivitis, then the clinician determines clinically the etiology of the patient's symptoms. Most commonly, the patient will then have either bacterial or allergic conjunctivitis.

BACTERIAL, VIRAL OR ALLERGIC?

BACTERIAL. If a patient's history and medical findings are more suggestive of bacterial

conjunctivitis, then we typically prescribe a topical antibiotic, which is most commonly a flouroquinolone. If the patient shows signs of lid involvement or cellulitis, we may prescribe oral antibiotics.

VIRAL. If the diagnostic test is positive for adenoviral conjunctivitis, we instruct the patient on ways to prevent contagion.

Most commonly, we suggest symptomatic treatment—such as artificial tears and cool compresses—for patient comfort. If the patient is experiencing a severe case, we may prescribe a mild steroid. Preliminary data has shown that prescribing ganciclovir (Zirgan, Bausch + Lomb) may be beneficial.[1]

There has also been some evidence that a diluted form of betadine may be useful.

If there are concerns that the patient may have a dual etiology of adenoviral conjunctivitis and something else, then we may prescribe an antibiotic, but that is generally not necessary.

ALLERGIC. Allergic conjunctivitis is often easier to differentiate from viral and bacterial because the vast majority of patients who have allergic conjunctivitis complain of itching, which often helps with diagnosis. That said, itching can also be present with viral conjunctivitis, so we typically conclude that the red eye is allergic in nature once a negative diagnostic test result is confirmed. If allergic conjunctivitis is diagnosed, we review the framework of the different medications used to treat allergies, such as antihistamine decongestant combinations, mast cell stabilizers, and anti-allergy compresses.

Treatment could be as simple as decreasing exposure to the allergen, but that may not always be an easy solution for the patient. We suggest symptomatic relief in the form of artificial tears and cool compresses to decrease the itching and swelling.

We also consider the possible negative effects of over-the-counter medication, such as decongestants and antihistamines. For example, oral agents can have a drying effect on the ocular surface.

Sometimes patients can have allergic conjunctivitis with other findings, such as dry eye. Cyclosporine (Restasis, Allergan) may be beneficial in improving the ocular surface.

If a patient has severe symptoms, we prescribe a topical steroid as well. Most commonly, I prescribe loteprednol etabonate ophthalmic suspension 0.2% (Alrex, Bausch + Lomb), because it is relatively mild. For severe cases, loteprednol etabonate ophthalmic gel 0.5% (Lotemax, Bausch + Lomb) is more appropriate.

If a patient has seasonal allergic conjunctivitis, he or she is better suited for a short-term treatment option. If a patient has perennial allergic conjunctivitis, I prescribe the steroid only when symptoms are present.

MAKING THE CALL

The most important aspect of a red eye protocol is that it gives patients a clear direction.

If the diagnostic test is positive, they may be out of work or school for 10 to 14 days. If it is negative then they can get back to their lives more quickly. It is not just the positive result that we benefit from, but the negative result benefits us even more. It gives patients the green light to return to their normal routine.

CONCLUSION

One of the most positive elements of utilizing a red eye protocol has been that patients perceive it as something that puts our practice at the forefront of high technology.

They recognize that their pediatricians and primary-care providers are utilizing rapid testing in their practices, and they appreciate that we are giving them more information as well. ■

Reference

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TRENDS

(*Continued from page 10*)

This survey highlights the need for improved treatments for those with year-round allergy. Like other studies, the authors note that an overwhelming majority of respondents experience both ocular and nasal symptoms, and many suffer with additional allergic symptomatologies. ■

(Table 1) Timing of allergic symptoms

When do you experience symptoms?	Spring	Summer	Fall	Winter	Year-Round
	49.3%	26.8%	39.5%	3.4%	38%

(Table 2) Frequency of common symptoms

What are your most common complaints associated with your eye allergy symptoms?	RANK		
	1st	2nd	3rd
Itching	70%	14.8%	3.1%
Watery eyes/tearing	8.2%	26%	16.3%
Redness	2.6%	19.9%	18.4%

(Table 3) Subject-initiated treatments (Figure 1 and Tables courtesy of Ora Inc.)

	YES	NO
Have you gone to an eye-care professional for ocular allergy symptoms?	36.1%	63.4%
Have you bought OTC eye allergy drops to treat ocular eye allergy symptoms?	50.7%	41.0%

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Special Report 〉 **OCULAR ALLERGY**

Why ocular allergy needs closer look

Diagnosis of allergic conjunctivitis may be overlooked without a proper evaluation

By Cheryl Guttman Krader; *Reviewed by Jodi Luchs, MD*

LONG ISLAND, NY ::

WHILE IT IS ONE of the most common conditions seen in daily practice, allergic conjunctivitis does not receive the attention it deserves in terms of its diagnosis and treatment, said Jodi Luchs, MD.

"Ocular allergy is not just a minor nuisance, and so it is important to key in on this condition," said Dr. Luchs, assistant clinical professor of ophthalmology, Hofstra University School of Medicine, Long Island, NY.

Dr. Luchs

"Those affected by ocular allergies can experience significant discomfort with their symptoms, problems with contact lens wear, difficulties with visual functioning affecting their work and leisure activities, and cosmetic issues that have psychosocial sequelae," he said.

UNCOVERING ALLERGIC CONJUNCTIVITIS

Diagnosis of allergic conjunctivitis may be challenging at times as it can co-exist with other ocular surface conditions that have overlapping signs and symptoms.

While it is generally true that itching is a hallmark sign of ocular allergy, patients affected may complain more about other manifestations, including grittiness, foreign body sensation, tearing, burning, and redness.

The usual signs of allergic conjunctivitis may be absent if the patient is self-medicating with over-the-counter products that make their eyes appear asymptomatic.

"Considering this information underscores the importance of taking the time for a careful history to diagnosis allergic conjunctivitis, technicians can be helpful in obtaining the information prior to the examination," Dr. Luchs said.

The ocular examination should focus on identifying the classic signs of allergic conjunctivitis:

- Conjunctival injection.
- Chemosis.
- Papillary reaction of palpebral conjunctiva.

Patients with ocular allergies may develop some ocular surface damage secondary to rubbing and other manual manipulation of the eyes, or have a reduced tear lake associated with use of oral anti-allergy products.

Clinicians should also be careful not to be misled by findings that are characteristic of dry eye disease.

"Remember that patients can have dry eye or blepharitis concomitant with allergic conjunctivitis, and that ocular allergy can masquerade as those conditions," Dr. Luchs said. "Therefore, the differential diagnosis may be a little more complex, but history is crucial for sorting out whether the patient has allergic conjunctivitis alone or in combination with some ocular surface disease."

COMPREHENSIVE MANAGEMENT

The goals of treatment for allergic conjunctivitis are to provide acute relief of bothersome signs and symptoms, and to avoid future exacerbations. Thus, dual-acting antihistamine/mast cell stabilizers are the treatment of choice.

Because patients with seasonal and perennial allergies need chronic treatment—since patient adherence is an important determinant of chronic treatment efficacy—once-daily dosing is an attractive attribute when selecting a product.

While there are several dual-acting, ophthalmic anti-allergy products, only two—olopatadine 0.2% (Pataday, Alcon Laboratories) and alcaftadine 0.25% (Lastacaft, Allergan)—are approved for once-daily dosing. Results from large, randomized, placebo-controlled clinical trials indicate that alcaftadine offers more persistent activity than olopatadine for relieving itch, Dr. Luchs noted.

The latter studies included about 275 patients and evaluated treatment efficacy using the antigen challenge model.

At 16 hours after drop instillation, the alcaftadine group had significantly lower mean itching scores at 3 minutes post-antigen exposure than both the placebo controls and the olopatadine group.

"These were not small studies, but multicenter trials with sufficient patient populations to satisfy statistical power requirements for phase III studies," Dr. Luchs said. "The results from the two studies were consistent with each other and show convincingly to me that alcaftadine has a benefit for controlling itch throughout the day."

A PROACTIVE APPROACH

Although patients with seasonal allergic conjunctivitis will present with their complaints during the relevant allergy season—and patients with perennial allergies may come in when experiencing an exacerbation—clinicians should probe for these conditions when patients are being seen for other reasons so that they can offer preventive intervention.

"Starting a dual-acting antihistamine/mast cell stabilizer proactively before antigen exposure, and continuing it throughout the allergy season, can help keep the patient's signs and symptoms under control," Dr. Luchs said. "These medications are extremely safe and effective for reducing the frequency and severity of allergic episodes and thereby perhaps reducing the need for topical steroids.

"Therefore, I prescribe them liberally and have a very low threshold for telling patients to start them prophylactically before allergy season begins," he said. ■

take-home

- **Diagnosis of allergic conjunctivitis, which can have a significant quality-of-life burden, may be overlooked or missed without a proper evaluation.**

How do you treat your patients with ocular allergies? Weigh in at **Facebook.com/OphthalmologyTimes**.

JODI LUCHS, MD

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Special Report 〉 **OCULAR ALLERGY**

Optimizing seasonal allergy control

Best approach targets early- and late-phase reactions to seasonal allergic conjunctivitis

By Cheryl Guttman Krader; *Reviewed by Gregg J. Berdy, MD, and Michael S. Blaiss, MD*

MANY DIFFERENT TREATMENTS can be used to control signs and symptoms of seasonal allergic conjunctivitis (SAC). From the perspective of both an allergist and an ophthalmologist, a dual-acting antihistamine/mast cell stabilizer should be the cornerstone of care.

"When patients are suffering with itching, watery eyes, and ocular redness from spring and fall allergies, the medications that work best to relieve these problems are the topical dual-acting antihistamine/mast cell stabilizers," said Michael S. Blaiss, MD, who is an allergy specialist and clinical professor of pediatrics and medicine, University of Tennessee Health Science Center, Memphis.

Dr. Blaiss

These agents mitigate the acute effects, which result from binding of histamine to its receptors and prevent the release of other mediators involved in the late-phase inflammatory reaction that also occurs in SAC, Dr. Blaiss said.

"An antihistamine alone will not decrease the inflammation," he said. "Decongestant eye drops affect only ocular redness and can have rebound effects.

"Agents that only act to stabilize mast cells must be dosed multiple times a day and used for several days before they work," he said.

Gregg J. Berdy, MD, FACS, assistant professor of clinical ophthalmology, Washington University School of Medicine, St. Louis, MO, said patients with SAC presenting for medical care often already tried nonpharmacologic strategies such as: allergen avoidance, cold compresses, and artificial tears, without success as well as over-the-counter anti-allergy medications.

IMMEDIATE RELIEF, CONTROLLING SYMPTOMS

"The primary aim in treating these patients is to give them immediate relief, but the chosen agent should also be effective for controlling future symptoms," Dr. Berdy said. "Among the medications available by prescription, . . . only the dual-acting antihistamine/mast cell stabilizers achieve both of these goals.

"Agents that only stabilize the mast cell are best used prior to the onset of symptoms, and a nonsteroidal anti-inflammatory drug has no effect on histamine and other preformed mediators released from the mast cells," he said.

However there are several dual-acting topical anti-allergy products to choose from, of which bepotastine besilate 1.5% (Bepreve, Bausch + Lomb) is one.

Clinical trial data show that bepotastine is highly efficacious in controlling SAC symptomatology.

"Testing using the conjunctival allergen challenge model showed bepotastine had a statistically significant benefit in relieving ocular itching within 3 minutes," Dr. Berdy said.

There is also data that show patients with allergic rhinoconjunctivitis using bepotastine achieved improvement in certain nasal symptoms, he said.

Safety data establish that bepotastine is very comfortable on instillation.

"In fact, in the clinical trials, bepotastine was rated as more comfortable than placebo," Dr. Berdy said.

Tolerability problems are also minimal with bepotastine, he said.

"Comfort is particularly important when treating pediatric patients who will resist treatment with a product that causes a lot of burning and stinging," he said.

BENEFITS OF CONVENIENT REGIMEN

Bepotastine is recommended for twice daily dosing, which is a convenient regimen but also can be beneficial for maintaining symptom control during times when allergen levels are very high, Dr. Blaiss said.

Some patients may find once-a-day administration sufficient for controlling their symptoms, Dr. Berdy said.

"I tell my patients to use one drop of bepotastine in each eye in the morning and let them judge the need for a second drop later in the day," he said.

Bepotastine also comes in a 10-ml bottle size, which can provide a 2-month supply for patients with just one co-payment, Dr. Blaiss said.

MANAGING ACUTE SAC FLARE

While a dual-acting antihistamine/mast cell stabilizer can act rapidly to relieve ocular itching, patients with severe SAC are best served by a topical corticosteroid.

The ester corticosteroid, loteprednol etabonate 0.2% (Alrex, Bausch + Lomb), is an option for managing an acute SAC flare.

"In my experience, patients respond rapidly to loteprednol etabonate 0.2%," Dr. Blaiss said. "After just a few weeks, their condition may be stabilized and then they can be managed on a more chronic basis using a dual-acting anti-allergy agent.

"However, I would refer patients who seem to require more persistent corticosteroid treatment to an ophthalmologist for further evaluation," he said.

There was only a 2% incidence of significant IOP elevation among about 900 patients treated with loteprednol etabonate 0.2% for ≥28 days in randomized, controlled clinical trials, according to the prescribing information.

In severe cases of SAC, Dr. Berdy said using the corticosteroid concomitantly with a dual-acting anti-allergy agent continues the latter medication after tapering patients off the corticosteroid.

However, long-term safety is excellent for the dual-acting anti-allergy agents, he said.

"Perennial allergic conjunctivitis is an underrecognized problem, but is important to diagnose and can be safely and effectively treated," he said. ■

take-home

- **Clinicians share their thoughts on the roles of a dual-acting antihistamine/mast cell stabilizer and topical ester corticosteroid in the management of seasonal allergic conjunctivitis.**

What are your thoughts? Go to **Facebook.com/OphthalmologyTimes** to let us know.

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Why early cataract surgery may help glaucoma later

Clear corneal phacoemulsification yields better IOP control, less dependence on medication

By Fred Gebhart; *Reviewed by Kuldev Singh, MD, MPH*

TAKE-HOME

- ***Cataract surgery not only can result in a reduction of IOP, it also provides benefits for future management of glaucoma.***

STANFORD, CA ::

A treatment opportunity exists to lower IOP by an average of 3 to 4 mm Hg for at least 3 years. But this treatment is not a drug, it is clear corneal phacoemulsification.

The treatment is generally safe, cost-effective, may improve vision in more than 90% of patients, and may improve the margin of safety for future glaucoma surgery.

If such a therapeutic profile could be achieved with an eye drop, it would be a blockbuster, said Kuldev Singh, MD, MPH, professor of ophthalmology and director, Glaucoma Service, Stanford University School of Medicine, Stanford, CA.

Dr. Singh

"Cataract surgery should be considered an IOP-lowering procedure," Dr. Singh said. "All things being equal, for the patient who is on the fence with regard to undergoing cataract surgery due to vision loss from lens opacification, the added benefit with regard to subsequent glaucoma care may help tip the balance in favor of surgery.

"Such treatment would not only be expected to improve vision, but on average, would result in better IOP control and/or reduction in dependence upon glaucoma medications," he said. "Cataract surgery can change the trajectory of glaucomatous disease."

TREATMENT BACKGROUND

Cataract surgery is already the most commonly performed IOP-lowering procedure.

While there are fewer than 100,000 glaucoma surgeries in the United States annually, Dr. Singh said, an estimated 15% of the 3.5 million patients who undergo cataract surgery also have primary open-angle glaucoma or ocular hypertension.

That is about 500,000 patients who typically benefit from lower IOP following phacoemulsification.

Multiple studies and meta-analyses have shown similar IOP-lowering effects from cataract surgery, Dr. Singh said.

Some ophthalmologists may not recognize this benefit and hold off on cataract surgery until vision loss is more severe, he said.

While there must be vision loss impacting some activities of daily living to consider cataract surgery, the visual threshold for surgery should be different in patients with coexistent glaucoma who will likely derive added benefit from lower postoperative IOP.

The positive impact on IOP has not yet been fully integrated in surgical decision-making.

BENEFITS OF ADDING IOP LOWERING

The time has come, Dr. Singh said, to expand the medical necessity for cataract surgery in patients who also have glaucoma and could benefit from the additional IOP lowering without adversely impacting future treatment options in most cases.

The IOP lowering with cataract surgery is blebless.

Several new adjunctive treatments with cataract surgery have been developed that also lower IOP without bleb formation, a profile that is clearly better than bleb-forming surgery in terms of long-term safety.

It is equally important to note that modern clear corneal temporal phacoemulsification leaves the superior conjunctiva untouched for future trabeculectomy and tube implantation.

"If you take out the cataract in a patient who may need glaucoma [surgery] in the future, you have really preserved all of your future options on the glaucoma surgery side," Dr. Singh said. "You have very little to lose and enormous benefits to gain by early, rather than late, cataract removal in such patients."

HOW IT WORKS

The key, he said, is to evaluate the visual need for cataract surgery. If patients meet the minimum threshold for cataract surgery, ophthalmologists can factor in the potential benefit of a sustained IOP lowering, particularly in those receiving glaucoma medications with associated costs, side effects, and issues of noncompliance.

"You may want to let your patients know that if you take out the cataract, their vision will improve and, on average, their IOP will be better controlled," Dr. Singh said. "For patients who are already [taking] glaucoma medication, they will likely be less dependent on eye drops after glaucoma surgery.

"You should also, however, share the possibility that IOP may increase in some individuals following cataract surgery and urgent glaucoma surgery may be required in a small subset of such patients," he said. "Those with severe and/or medically uncontrolled glaucoma may sometimes require glaucoma surgery prior to cataract surgery or combined phaco trabeculectomy."

LOOKING TO THE FUTURE

The rationale for early cataract surgery will only become stronger as new minimally invasive devices to lower IOP become available.

Some of these devices have already been approved for use, and others are still at various stages of the regulatory approval process in the United States. The extent to which these devices and procedures lower IOP beyond the effect of phacoemulsification alone will impact the threshold for the performance of cataract surgery, Dr. Singh said. ■

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Dr. Singh is a consultant to Alcon Laboratories, Allergan, Bausch + Lomb, Ivantis, and Transcend Medical.

Benefits of anti-VEGF therapy for DME durable to 3 years

Functional improvement was decreased by treatment delay, research shows

By Cheryl Guttman Krader; *Reviewed by Leonard Feiner, MD, PhD*

TAKE-HOME

- ***Patients who receive intravitreal ranibizumab (Lucentis, Genentech) for treatment of diabetic macular edema over a 3-year period achieved rapid improvements in vision and edema.***

TEANECK, NJ ::

Monthly injections of intravitreal ranibizumab (Lucentis, Genentech) for diabetic macular edema (DME) result in functional and anatomic improvements that are maintained for at least 3 years and without the emergence of new safety signals, recent research has found.

Findings from 36 months of follow-up in the phase III RISE and RIDE trials also indicated a physiologic benefit of the anti-vascular endothelial growth factor (VEGF) treatment, said Leonard Feiner, MD, PhD, who is in private practice, Retina Associates of New Jersey, Teaneck, NJ.

The trials showed reduction in area of leakage on fluorescein angiography, which continued to increase over time. Earlier treatment initiation may result in better outcomes as well.

"Laser photocoagulation is beneficial for the treatment of DME and reduces the risk of vision loss by about 50%," Dr. Feiner said. "However, few patients experience visual benefit.

"As in age-related macular degeneration and retinal vein occlusion, ranibizumab redefines the standard of care for patients with DME," he said.

ABOUT THE TRIALS

RISE and RIDE enrolled about 750 patients with best-corrected visual acuity (BCVA) of 20/40 to 20/320 and optical coherence tomography central subfield thickness ≥275 µm.

They were randomly assigned 1:1:1 to monthly intravitreal injection with ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham. All patients could receive laser photocoagulation beginning at month 3 if their vision or macular edema was not improving.

The primary endpoint was at 24 months, and thereafter, patients in the sham arm were eligible to be crossed over to ranibizumab.

More than 80% of patients in each treatment arm completed follow-up to 24 months, and retention at 36 months ranged from 73% in the sham arm to about 78.5% in the ranibizumab arms.

TRIAL RESULTS

Patients originally treated with ranibizumab experienced rapid improvement in BCVA, with notable vision gain seen as early as 7 days, on average.

At 24 months, BCVA had improved by slightly more than 2 lines across all ranibizumab arms and the gains persisted at 36 months.

After crossover to ranibizumab, patients in the sham arm also had an improvement in vision. However, the gain from BCVA at 24 months was only about 2 letters based on an intent-to-treat analysis, with last observation carried forward.

Only about 3 letters in an analysis included only the sham patients who received at least one ranibizumab injection after month 24.

"Findings from subgroup analyses showed that the benefits of ranibizumab treatment for improving vision were consistent," Dr. Feiner said. "However, as expected, patients whose central foveal thickness was 450 µm or greater at baseline had more BCVA improvement than their counterparts with less edema at enrollment."

Analyses of changes in central foveal thickness showing early reductions were maintained with continued ranibizumab treatment.

The crossover to ranibizumab among sham patients resulted in drying of macular edema despite the limited vision benefit.

ANALYSES

Evaluation of changes in area of fluorescein angiogram leakage provided evidence of the physiologic benefit of ranibizumab and showed a steady incremental increase in the proportion of patients with complete absence of leakage.

"This effect of the anti-VEGF treatment does not seem to have peaked yet at 36 months," Dr. Feiner said.

Patients who were also treated with ranibizumab had less progression (by 2 or 3 steps on the ETDRS retinopathy severity scale) of their background diabetic retinopathy than those who were in the sham group.

Patients in the ranibizumab groups also had higher rates of improvement in diabetic retinopathy than those in the sham group.

"This suggested that treatment with ranibizumab may lead to some disease-modifying effects in the eyes of patients with DME and warrants further study," Dr. Feiner said.

While the phase III studies are not powered to evaluate safety, Dr. Feiner said he found that adverse event data showed ocular safety was generally balanced between groups.

The few cases of endophthalmitis occurred only among ranibizumab-treated patients and the rate of vitreous hemorrhage was higher in sham-treated patients.

Rates of arterial thrombotic events and death at 36 months were also slightly higher in the ranibizumab arms versus the sham-treated control, as were rates of serious adverse events potentially related to systemic VEGF inhibition.

"The latter events occurred at a higher rate with the 0.5-mg dose of ranibizumab compared with the 0.3-mg arm, which, along with the finding of similar efficacy between doses, were some of the primary motivations for Genentech choosing to file the 0.3-mg dose for FDA approval," Dr. Feiner said. ■

LEONARD FEINER, MD, PHD

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Dr. Feiner is a consultant to and serves on the speakers' bureau for Genentech.

When patients with AMD require cataract surgery

Various practices, drugs should be weighed carefully to decrease postop complications

By Lynda Charters; *Reviewed by Timothy W. Olsen, MD*

TAKE-HOME

- ***There are numerous methods and factors surgeons should examine for patients with age-related macular degeneration who require cataract surgery to avoid future problems.***

ATLANTA ::

Treating patients with age-related macular degeneration (AMD) who need cataract surgery becomes even more complicated when the effect of other potential drug use is considered, said Timothy W. Olsen, MD.

PROPHYLACTIC ANTIBIOTICS

Cataract surgery is one of the most common ophthalmic procedures performed, while topical antibiotics have traditionally been an important part of postoperative care.

Cataract surgeons should ask patients being treated with intravitreal injections for AMD if they are also receiving routine antibiotics after the injections from the retina surgeon.

Dr. Olsen

"When patients are asked to use prophylactic antibiotics by the retina specialist, this is not typically something that happens only once," said Dr. Olsen, F. Phinizy Calhoun Sr. Professor and chairman, Department of Ophthalmology, Emory University, Atlanta. "Some retina specialists still routinely administer topical antibiotics following each injection.

"Some suggest administration for 3 days following each injection," he said. "While this is becoming less common, such patients can receive up to 24 injections during a 2-year period and (this) represents overuse of broad-spectrum antibiotics."

A recent study[1] of ocular bacterial flora found that eyes treated with frequent antibiotics had significantly higher antibiotic resistance as measured by minimum inhibitory concentrations.

"Eyes treated with topical antibiotics are developing more resistance to bacterial strains," Dr. Olsen said. "We are probably doing very little good for these patients and may actually be creating a harmful, more resistant ocular flora."

The study recommended that routine prophylactic use of antibiotics after intravitreal injections be discouraged—a position also endorsed by the American Academy of Ophthalmology and the Choosing Wisely campaign, led by the ABIM Foundation.

Should these patients undergo cataract surgery and develop endophthalmitis, the infecting agent may theoretically originate from a more drug-resistant strain.

> 'Eyes treated with topical antibiotics are developing more resistance to bacterial strains.'
>
> — Timothy W. Olsen, MD

ANTI-VEGF DRUGS

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs for AMD are characterized by peak-and-trough pharmacokinetics in the vitreous. The peak-and-trough effect raises the question about the optimal time to perform cataract surgery.

Pharmacologically, Dr. Olsen said, the ideal time for cataract surgery may be near the end of the anti-VEGF cycle, which is closer to the trough. For example, cataract surgery 1 week before the next scheduled injection would minimize the anti-VEGF drug dilution that occurs as a result of the fluidics used intraoperatively.

The eye would have the chance to heal for a week, with a lower-level tissue anti-VEGF level and be able to tolerate the next scheduled injection.

In contrast, cataract surgery 1 week after an anti-VEGF injection would risk dilution of the peak pharmacokinetic effect of the anti-VEGF agent.

Cataract surgeons have expressed a valid concern that an anti-VEGF injection 1 week after cataract surgery could risk opening or dehiscence of the cataract incision.

A compromise may be to place a 10-0 nylon suture in the cataract wound, give the injections as scheduled, and then eventually remove the suture after the cataract wound has stabilized.

Another option is to time the cataract surgery to correspond with the next scheduled anti-VEGF injection, and ask the cataract surgeon to deliver the agent at the conclusion of the case.

Despite effective treatment using anti-VEGF agents, AMD continues to progress.

Studies[2] suggest that at 5 years after treatment initiation, patients' vision slowly declines.

EXAMINATION OF FINDINGS

To help cataract surgeons gauge the patients' status in 5 years, Dr. Olsen considered a patient with large drusen and pigment clumping who needed to undergo cataract surgery.

Based on the simplified grading scale,[3] the patient likely had a 50%, 5-year risk of progression to advanced disease in at least one eye.

Dr. Olsen underscored the importance of risk-assessing the macula and ensuring that at-risk patients take antioxidant supplements

Continues on page 21 : ***AMD***

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AMD

(Continued from page 19)

(Age-Related Eye Disease Study [AREDS]) and adhere to a healthy lifestyle that includes green leafy vegetables, fresh fruit, fish, lower fat, and avoidance of smoking.

In another patient with non-central geographic atrophy (GA), Dr. Olsen said a point to consider is that non-central GA can progress to involve the central macula, making the choice of a multifocal IOL over a monofocal lens a poor choice. The AREDS study[4] indicated there is an average 2-mm/year expansion of GA. Such a patient should not be considered a good candidate for a multifocal IOL.

A patient with GA, pigmentary changes, and large soft drusen is at risk for bilateral disease.

Another consideration for patients with advanced AMD and cataract would be to discuss the FDA-approved ophthalmic telescope implant (Implantable Miniature Telescope [by Dr. Isaac Lipshitz], VisionCare). Proper rehabilitation assessment is critical for identifying good candidates for the telescope implant.

The role of a yellow-tinted IOL may also offer theoretic advantages for slowing AMD progression, yet this claim is unsupported by data.

Some argue[5] that a yellow tint diminishes night or dark-adapted vision, interferes with the diurnal cycle, promotes affective disorders (depression), and may limit contrast sensitivity in certain conditions.

"Lens selection is important in patients with AMD, and informing patients about their individual risk of progression is critical," Dr. Olsen said. "Surgical pre-assessment using visual rehabilitation measures is essential when selecting patients who are considered candidates for the [telescope implant]."

EXPERIMENTAL METHODS OF DRUG DELIVERY

Various future options, such as microcannulae and microneedles, could be used to access the suprachoroidal space—a technology developed as a joint project among researchers at Emory, Georgia Tech, and the University of Minnesota, Dr. Olsen noted.

These technologies are entering developmental stages and early clinical trials with industry. Other options in the pipeline include:

- Punctal plugs loaded with pharmaceuticals.
- The lens capsule as a reservoir for drug release.
- IOL implant itself as a drug repository.
- Nanoparticles used in novel and innovative ways.

"It is important to ask patients about use of topical antibiotic prophylaxis," Dr. Olsen said. "The timing of cataract surgery in relation to administration of anti-VEGF therapy should be planned and coordinated effectively.

"For patients with AMD, risk-assess, communicate risk, and encourage patients to use antioxidant supplements and live a healthy lifestyle," he said. ■

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Adding femtosecond laser to practice

From Staff Reports

MADISON, WI ::

OPHTHALMOLOGISTS ARE NEARING a crossroads with the replacement of phaco by femtosecond laser technology.

Among the issues are cost, charges to patients, acceptance of the technology by other practices, and outcomes, said John Vukich, MD, surgical director, Davis Duehr Dean Center for Refractive Surgery, Madison, WI.

The femtosecond laser costs from $400,000 to $550,000; service fees annually are about 10% of the purchase price; and each surgery has a per-use fee of $350 to $450. The fee passed along to the patient must be economically viable to both the patient and the practice.

A survey of physicians who perform femtosecond laser cataract surgery included 65 of 134 eligible femtosecond laser centers in the United States and 205 surgeons who performed more than 278,000 cataract cases; of these surgeries, 23% and 22% were premium procedures in 2012 and 2013, respectively (a total of 37,600 surgeries).

Twenty percent of conventional IOL implantations were performed using the femtosecond laser, Dr. Vukich noted.

"This was a surprise, because many expected the use of the femtosecond laser to be tied to premium IOLs," he said. "Another surprise was that 55% of toric IOLs were implanted using the femtosecond laser; and 74% of presbyopic IOLs were implanted using the femtosecond laser."

The survey found that the mean acquisition cost was about $438,000; the services fees were about $165,000; and the 5-year cost was more than $600,000. The average increase in the cost per case was $859 with a per-case cost of $327, which resulted in a per-case margin of $532. Surgeons must perform about 1,100 femtosecond laser cases to break even, which means they must perform about 227 cases annually and 19 to 20 cases monthly, Dr. Vukich said.

With these numbers, one-third of the practice is involved with the femtosecond laser in order to break even, he explained.

The actual trend in utilization of the femtosecond laser indicated that most practices were at about 25% to 30% penetration within the first year of use of the laser, and most were at 25% within 3 months. Of the practices that initially purchased a femtosecond laser, about 71% were breaking even and 8% were near the break-even point. Multisurgeon centers fared much better in recouping the initial costs of the laser compared with single-surgeon centers. ■

Could femto laser in cataract surgery become a necessity?

In specific cases, certain advantages of application could surpass the human hand

By Liz Meszaros; *Reviewed by Arun C. Gulani, MD*

TAKE-HOME

- ***The financial feasibility of using only one laser for all procedures is a given. Arun C. Gulani, MD, takes this one step further, arguing that perhaps the future may hold cases in which use of the femtosecond laser is becoming a standard-of-care concept.***

JACKSONVILLE, FL ::

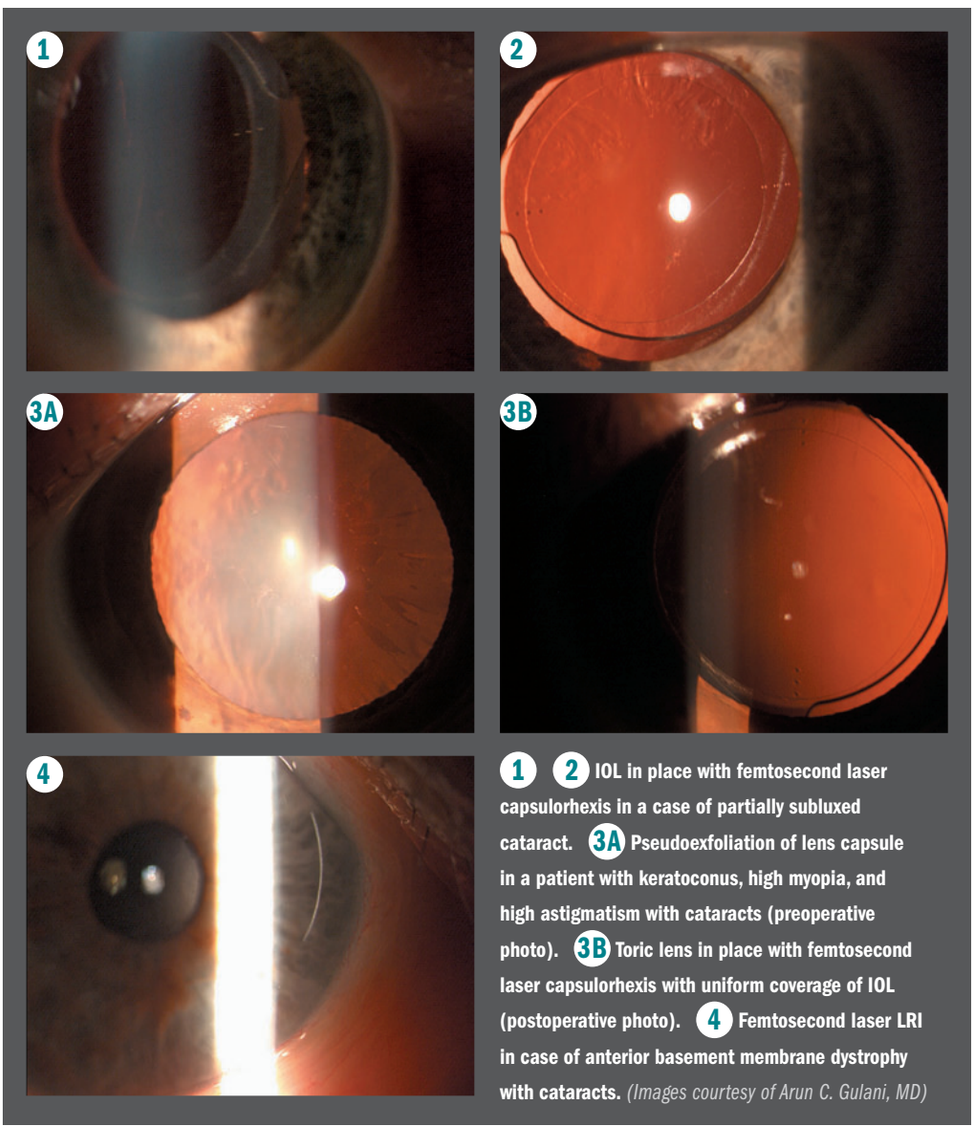
Many surgeons predict that soon, all ocular surgery will be performed with lasers. Joining the excimer, argon, and Nd:YAG lasers—which have established their benefits in laser vision, retina, and glaucoma procedures—is the femtosecond laser, currently used in the United States for LASIK procedures.

"We know that femtosecond lasers have brought a paradigm shift in cataract surgery," said Arun C. Gulani, MD, founder and chief surgeon of the Gulani Vision Institute, Jacksonville, FL. "It is the wave of the future, in which lasers will do everything.

Dr. Gulani

"Now that cataract femtosecond lasers have become available, the concept becomes what I have always envisioned—that an anterior segment surgeon will never have to leave the office," said Dr. Gulani, having experience with most femtosecond lasers, years before FDA approval in the United States with his international privileges. "An anterior segment surgeon can perform all diagnostics, surgery, and real-time refractive alignment with fine tuning in one sitting in the office."

The financial feasibility of using only one laser for all procedures is a given, but Dr. Gulani takes this one step further, arguing the future may hold cases in which the femtosecond laser is a necessary, standard-of-care concept.



1 2 IOL in place with femtosecond laser capsulorhexis in a case of partially subluxed cataract. 3A Pseudoexfoliation of lens capsule in a patient with keratoconus, high myopia, and high astigmatism with cataracts (preoperative photo). 3B Toric lens in place with femtosecond laser capsulorhexis with uniform coverage of IOL (postoperative photo). 4 Femtosecond laser LRI in case of anterior basement membrane dystrophy with cataracts. *(Images courtesy of Arun C. Gulani, MD)*

CATARACT CAPABILITY

Currently, at least four femtosecond lasers are approved in the United States for performing corneal incisions, anterior capsulotomy, limbal relaxing incisions (LRIs), and lens fragmentation in cataract procedures. Among the advantages the femtosecond laser brings to these procedures is an improved and consistent safety and predictability profile.

"The femtosecond laser right now does our incision, astigmatism LRIs, capsulorhexis, and lens fragmentation," Dr. Gulani said. "The concept here is—in cases such as pseudoexfoliation of the capsule, minimally subluxed cataracts, and mature cataracts—doing the capsulorhexis is the Achilles' heel of the eye surgeon. No matter how gifted we are, this is where

Continues on page 24 : ***Necessity***

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NECESSITY

(Continued from page 22)

we get worried because the capsule may just tear in the wrong direction and then the case is out of control.

"In these cases, having something as reliable, consistent, and predictable as the femtosecond laser literally takes the edge away," he said. "Once you have a great rhexis in a mature cataract, not only does it set your stage, but it also decompresses the capsular bag to avoid the 'Argentinian flag sign' as an ominous sign of impending disaster."

In pseudoexfoliation, it makes it much more controlled and safe.

> 'The concept becomes what I have always envisioned—that an anterior segment surgeon will never have to leave the office.' *– Arun C Gulani, MD*

Similarly, in partial subluxed cataract as well, Dr. Gulani continued, it could give a perfect rhexis so the surgeon aligns it to the lens and perhaps plans a capsular tension ring, for example, and then it is done.

"These are cases where I feel literally that using a femtosecond laser becomes mandated with today's availability of femtosecond lasers. But could not doing it with femtosecond laser be considered a lack of standard of care?" he posited.

Lesser indications that could mandate a femtosecond laser include cases of anterior corneal dystrophy and Fuchs' dystrophy, where the creation of LRIs could rip the loose epithelium (abrading of the epithelium) so the patient then may complain of foreign body sensation the next day, despite a perfect cataract surgery and vision outcome.

"In these cases, what is beautiful with the femtosecond laser is that it creates the incision intrastromally," Dr. Gulani said.

The epithelium is therefore tightly apposed and mostly intact, and the LRIs are done predictably and can be opened next day in a controlled fashion with a specifically designed instrument, Dr. Gulani said.

He is currently designing a femtosecond laser cataract instrument set to this end in collaboration with Bausch + Lomb.

CASE REPORT

In one of his cases, the use of the femtosecond laser was particularly beneficial, Dr. Gulani noted. A male aged 58 years was referred with stable keratoconus, high astigmatism, pseudoexfoliation, cataract, and high myopia. By including the use of the femtosecond laser, Dr. Gulani was able to provide exact, consistent, and predictable treatment for this otherwise challenging case.

Involving the femtosecond laser made his course so much easier, Dr. Gulani said, because he wasn't worried about the patient's pseudoexfoliation in a very deep anterior chamber.

"I could accurately plan the rhexis for my two opposing desires—one to have a rhexis large enough to flip the cataract out of the bag and emulsify in the anterior chamber, and second to have it small enough to have a rim around the entire lens implant to maintain a stable and snug, rotation-free atmosphere for this toric lens with high astigmatism responsibility," he explained.

"Surely, I could have managed this case like many others before him using my handheld instruments," Dr. Gulani concluded. "But with the availability of the femtosecond laser today, I felt as if I would have deprived him of what could be considered his 'right of way.'" ■

Suggested reading

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Is use of the femtosecond laser becoming a standard of care? Weigh in at **Facebook.com/OphthalmologyTimes**.

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How to make the right lens choice

ECPs have a duty to warn patients of the safest and best lens material

By Rose Schneider, *Content Specialist,* Ophthalmology Times

Types of safety lenses

Glass lenses

- Scratch-resistant
- Can be made with a corrective prescription
- If the lens is scratched, it should be replaced immediately

Plastic lenses

- Are lightweight
- Protect against welding splatter
- Are not likely to fog

Polycarbonate lenses

- Are lightweight
- Protect against welding splatter
- Are not likely to fog
- Can be stronger, more impact-resistant, and less scratch-resistant than glass depending on the situation and the lens itself

Table courtesy of The Vision Council

Eye-care professionals (ECPs) have an ethical as well as legal responsibility to inform their patients regarding lens material options and safety, said Pamela Miller, OD, JD, of Highland, CA.

However, patients may still be unfamiliar with their choices.

According to a PPG Industries-sponsored study, while patients have an interest in lenses with various features, they need more education on their options by ECPs.

Dr. Miller

"Survey respondents reported a tendency to defer to an ECP's recommendation when selecting a lens material," the 2012 study said. "The research indicated a general lack of awareness about lens material options, with nearly 67% of respondents reporting that they didn't know which lens material was used to make their eyeglasses."

While Dr. Miller said she is unsure how often ECPs or their staff spend time going through the various lens options and safety with their patients, she believes they ought to—especially when those patients are children, as they are more prone to injury.

"It's just part of how you take care of patients," Dr. Miller said of the ethical practice, Duty to Warn, which is an integral part of that process.

BACKSTORY OF THE CONCEPT

The Duty to Warn concept, in regard to the eyecare field, originated in the late 1980s following several court cases involving patients who were injured when their eyeglasses broke.

The courts found that ECPs were liable

Continues on page 29 : ***Duty to warn***

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In Brief

FROM STAFF REPORTS

Merging businesses

SUPERIOR VISION, BLOCK VISION TO COMBINE

RANCHO CORDOVA, CA AND LINTHICUM, MD :: **SUPERIOR VISION AND BLOCK VISION** announced they are merging their businesses, according to representatives in a joint statement.

"The end result is a comprehensive eye-care company with member-centric solutions for the commercial, Medicare, and Medicaid markets, encompassing the full range of wellness vision and medical/surgical eye-care programs," said Kirk Rothrock, president of Superior Visions.

The combined company will provide vision benefit plans to more than 8.5 million members nationwide, as well as a provider network surpassing 55,000 access points.

"We are excited at the opportunity to join forces with a company that so closely matches our philosophy of being focused solely on vision and eye health," said Andrew Alcorn, president and chief executive officer of Block Vision.

Both companies will also join management forces and service delivery that will respond to the varying presence of vision benefits within the Affordable Care Act and related public/private exchanges. The agreement is expected to be completed within the next few months.

Lens production marker

TRANSITIONS OPTICAL CELEBRATES MILESTONE

(Photo courtesy of Transitions Optical)

PINELLAS PARK, FL :: **TRANSITIONS OPTICAL** recently announced the production of its Transitions Vantage lenses has reached 1 million.

The lenses, which are designed to darken and polarize upon UV exposure for crisper and sharper vision, have had increased sales since their launch in May 2012.

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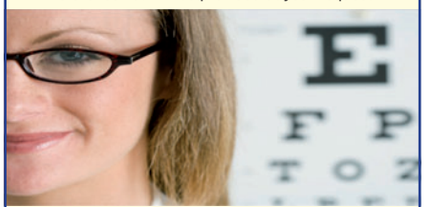

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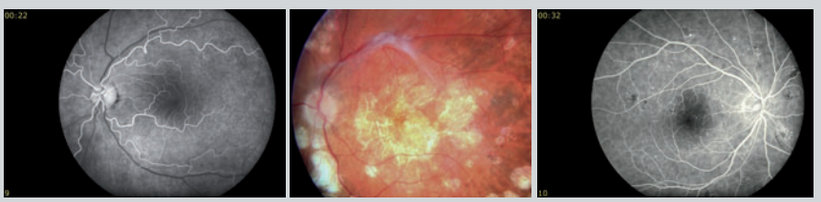

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DUTY TO WARN

(Continued from page 25)

TAKE-HOME

- ***There is a moralistic responsibility that all eye-care professionals should follow to make sure their patients choose the correct eyewear to prevent injury, especially when the patients are children.***

for the injuries sustained from the eyewear because either higher-impact-resistant lens material was available in the patient's correction or the patient was not informed of viable options.

Soon after, Dr. Miller, along with Joe Bruneni, FNAO, of Vision Consultants, helped develop the Duty to Warn kit—an informative package on the concept—that is sent to ECPs.

ECPs then began following the Duty to Warn procedure, which includes:

- Informing patients about the higher-impact-resistant lenses
- Going through the pros and cons of each product
- Having the patients sign a form stating they were properly informed and have either chosen to take the ECP's suggestion or knowingly refuse it.

More than 20 years later, Dr. Miller said the concept is as important as ever for ECPs.

"As knowledge increases and products improve and increase, our obligations pretty much increase as well," she said. "Your job is to protect your patient."

PROTECTING CHILDREN FROM EYE INJURIES

That obligation becomes even more important when dealing with children, Dr. Miller said.

There are more than 100,000 people who sustain eye injuries every year and more than half of those injured are children, according to the American Academy of Ophthalmology (AAO).

"Children are at a higher risk of injury, children are not as careful," Dr. Miller said. "They are more prone to injury (and) they are more heavily involved in sports."

More than 42,000 sports- and recreation-related eye injuries were reported in 2000, according to the American Academy of Pediatrics (AAP) and AAO.

Of that total, AAP and AAO said 72% of the injuries occurred in individuals aged fewer than 25 years old, 43% occurred in those aged fewer than 15 years old, and 8% occurred in children aged fewer than 5 years old.

"Although eye protectors cannot eliminate the risk of injury, appropriate eye protectors have been found to reduce the risk of significant eye injury by at least 90% when properly fitted," AAP and AAO jointly said.

POLYCARBONATE OR HIGH INDEX BEST CHOICE FOR CHILDREN

In patients who are aged fewer than 18 years, Dr. Miller said ECPs should always recommend the higher-impact-resistant lenses, such as polycarbonate.

"In my practice, we basically automatically prescribe polycarbonate for children," she said.

There are some parents, however, who are apprehensive to purchase polycarbonate lenses for their child, Dr. Miller said, despite strong research suggesting they are the safest lenses for young people.

"Polycarbonate lenses are thinner and lighter than standard plastic varieties, but much more durable," according to The Vision Council. "Polycarbonate is ideal for strong prescriptions because it corrects vision without adding thickness, which can distort the wearer's appearance.

"Best of all, polycarbonate lenses are virtually unbreakable, making them a great choice for kids and active adults," the council said.

But the cost of polycarbonate lenses, Dr. Miller said, most commonly drives parents toward the more cheaper, yet less safe eyewear options.

"CR-39 is more likely to break and shatter, it is not as safe," she said. "(Unfortunately) it always comes down to money."

There is a $30 to $65 upcharge difference from the CR-39 to the polycarbonate lens for a standard single-vision prescription, said Arthur De Gennaro, president of Arthur De Gennaro & Associates LLC, a Lexington, SC-based ophthalmic practice management firm that specializes in optical dispensing issues.

If parents insist on CR-39, or lenses other than polycarbonate for their child, Dr. Miller said it is the ECP's responsibility to make the parents' decision clear to them, which is when Duty to Warn comes into place.

"It is the obligation of the practitioner to warn and advise the patient—and in this case the patient and the parent or guardian—of the pros and cons of a particular product," Dr. Miller said. "(But) the bottom line is the parent or guardian is under no obligation to accept your recommendation, but you're under obligation to lay them out."

In abiding by the practice, Dr. Miller said ECPs are enabling the decision-maker, in this case the parents, to make an informed decision.

"It (Duty to Warn) puts the person who has more information or more knowledge in an obligatory position of warning the person who will be receiving the materials," she said.

While ECPs are not legally bound to follow Duty to Warn—as there are no laws mandating they do—Dr. Miller said the practice should be followed simply because it is the right thing to do.

"It becomes an ethical consideration," Dr. Miller said. "You don't have to do it, you don't have to do anything.

"(But) it's the appropriate thing to do to protect the patient, as well as your practice," she said. ■

How do you decide on a lens material?

	Percent
I will always choose the lens that offers the best vision, no matter what.	10.2
A combination of lens attributes is important (optics, thinness, lightweight, impact-resistance, etc.).	38.4
The price of the lens is my primary concern.	21.0
I will always choose the lens material my eye-care professional recommends to me.	21.2
Don't know.	9.2

Online survey of 500 adult eyeglass wearers with dependent children, conducted on behalf of PPG Industries Inc., by Lightspeed Research, March 1 to 5, 2012. *(Table courtesy of PPG Industries Inc.)*

How do you ensure patients make the appropriate lens choice for their safety? Let us know at **Facebook.com/OphthalmologyTimes.**

PAMELA MILLER, OD, JD

E: *drpam@omnivision.com*

Dr. Miller has no financial interest in any products or companies mentioned in this article.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into the affected eye(s) twice a day (BID).(2)

--------DOSAGE FORMS AND STRENGTHS---------
Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE® should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE®. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION
Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2. DOSAGE AND ADMINISTRATION

Instill one drop of BEPREVE® into the affected eye(s) twice a day (BID).

3. DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution containing bepotastine besilate 1.5%.

4. CONTRAINDICATIONS

BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients [see Adverse Reactions (6.2)].

5. WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

To minimize contaminating the dropper tip and and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use

Patients should be advised not to wear a contact lens if their eye is red. BEPREVE® should not be used to treat contact lens-related irritation. BEPREVE® should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of of BEPREVE®.

5.3 Topical Ophthalmic Use Only

BEPREVE® is for topical ophthalmic use only.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post Marketing Experience

Hypersensitivity reactions have been reported rarely [two (2) possibly related cases for an incidence of 0.00006%] during the post-marketing use of BEPREVE®. Because this reaction is reported voluntarily from a population of unknown size, the actual incidence cannot be verified. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral does up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1000 mg/kg/day, however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3300 times the topical ocular use in humans). The concentration of radiolabeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

There are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Following a single 3 mg/kg oral dose of radio-labeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 µg eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use

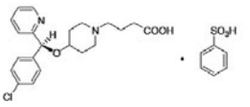
Safety and efficacy of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

8.5 Geriatric Use

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

11. DESCRIPTION

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE® contains 15 mg of bepotastine besilate. Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bepotastine is a topically active, direct H_1 receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics

Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four time daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were the below quantifiable limit (2ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use.

The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for human topical use).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3300 times the systemic concentration anticipated for topical ocular use in humans).

14. CLINICAL STUDIES

Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE®.

The safety of BEPREVE® was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16. HOW SUPPLIED/STORAGE AND HANDLING

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following sizes:

5 mL (NDC 67425-007-50)
10 mL (NDC 67425-007-75)

STORAGE
Store at 15° – 25°C (59° – 77°F).

17. PATIENT COUNSELING INFORMATION

17.1 Topical Ophthalmic Use Only

For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip

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

17.3 Concomitant Use of Contact Lenses

Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE® should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE®.

Manufactured for: ISTA Pharmaceuticals, Inc.
Irvine, CA 92618

By: Bausch & Lomb Incorporated
Tampa, FL 33637

Under license from:
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Osaka, Japan 541-0046

U.S. Patents: 6,307,052; 6,780,877

For allergic conjunctivitis[1]

THE POWER TO CALM THE ITCH

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INDICATION AND USAGE

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

IMPORTANT RISK INFORMATION

BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens–related irritation. Remove contact lenses prior to instillation of BEPREVE®.

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

Made by the trusted eye-care specialists at BAUSCH + LOMB

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

Reference: 1. BEPREVE [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc; 2012.

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

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1. Bausch & Lomb Incorporated Study #658 - "A Prospective Multicenter Clinical Study to Evaluate the Safety and Effectiveness of a Bausch + Lomb One Piece Hydrophobic Acrylic Intraocular Lens in Subjects Undergoing Cataract Extraction." Final Clinical Study Report, dated 24 Aug 2011. **2.** Tetz MR, Werner L, Schwahn-Bendig S, Batlle JF. A prospective clinical study to quantify glistenings in a new hydrophobic acrylic IOL. Presented at: American Society of Cataract and Refractive Surgery (ASCRS) Symposium & Congress; April 3-8, 2009; San Francisco, CA. **3.** enVista® Directions for Use. **4.** Santhiago MR, Netto MV, Barreto J Jr, et al. Wavefront analysis, contrast sensitivity, and depth of focus after cataract surgery with aspherical intraocular lens implantation. *Am J Ophthalmol.* 2010;149(3):383-389. **5.** Pepose JS, Qazi MA, Edwards KH, Sanderson JP, Sarver EJ. Comparison of contrast sensitivity, depth of field and ocular wavefront aberrations in eyes with an IOL with zero versus positive spherical aberration. *Graefe's Arch Clin Exp Ophthalmol.* 2009;247(7):965-973. **6.** Johansson B, Sundelin S, Wikberg-Matsson A, Unsbo P, Behndig A. Visual and optical performance of the Akreos® Adapt Advanced Optics and Tecnis Z9000 intraocular lenses: Swedish multicenter study. *J Cataract Refract Surg.* 2007;33(9):1565-1572. **7.** Nishi O, Nishi K, Osakabe Y. Effect of intraocular lenses on preventing posterior capsule opacification: design versus material. *J Cataract Refract Surg.* 2004;30(10):2170-2176.

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