Ocular Surface Review: Mucin Dysfunction, *p. 96* • **Urgent Care:** Vitreous Hemorrhage, *p. 100*

REVIEW® of OPTOMETRY

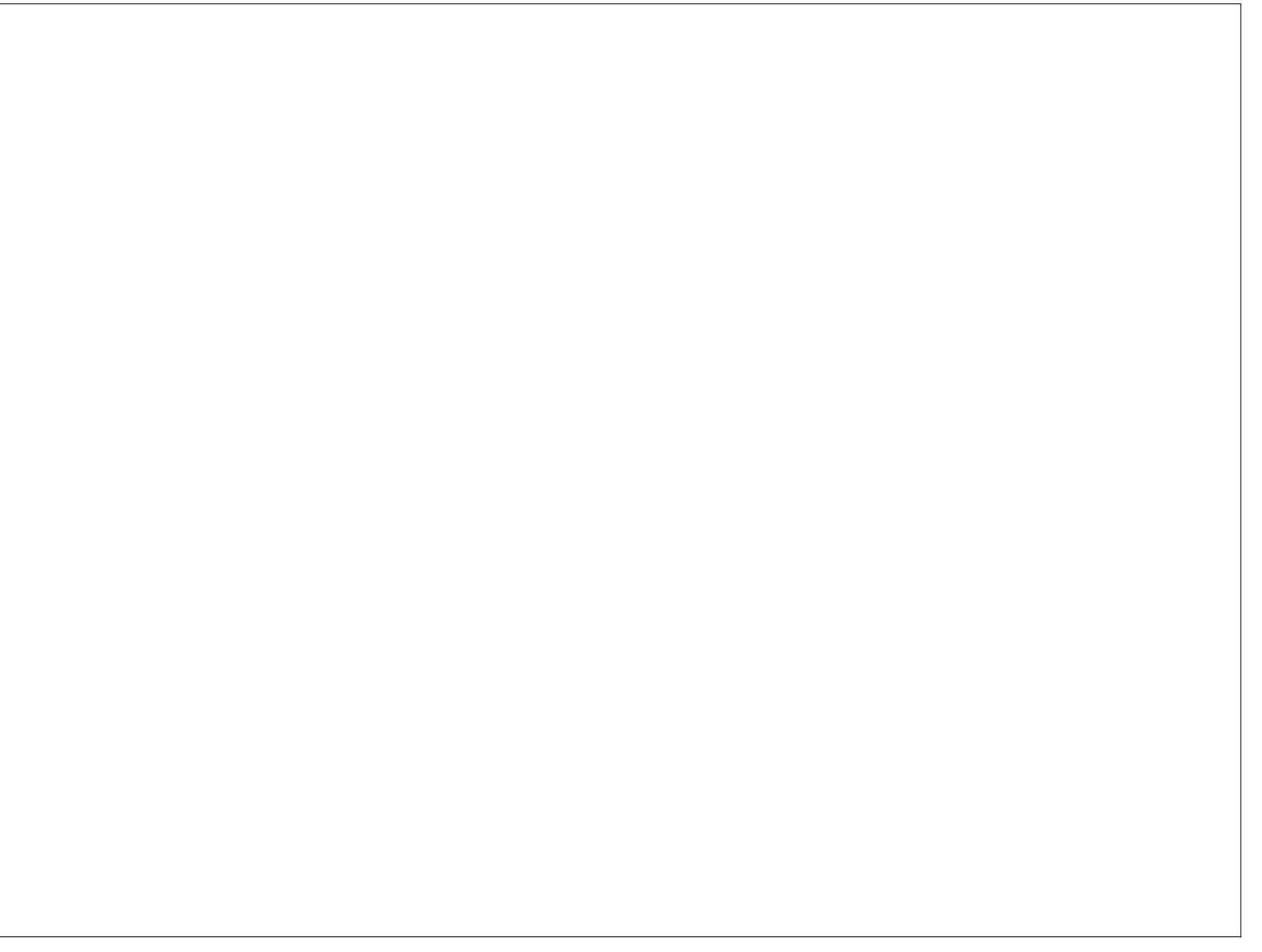
15TH ANNUAL PHARMACEUTICALS REPORT

March 15, 2022 • reviewofoptometry.com

Leadership in clinical care

FIND THE RIGHT MIX

New meds give you more control than ever before over treatment decisions—and outcomes.



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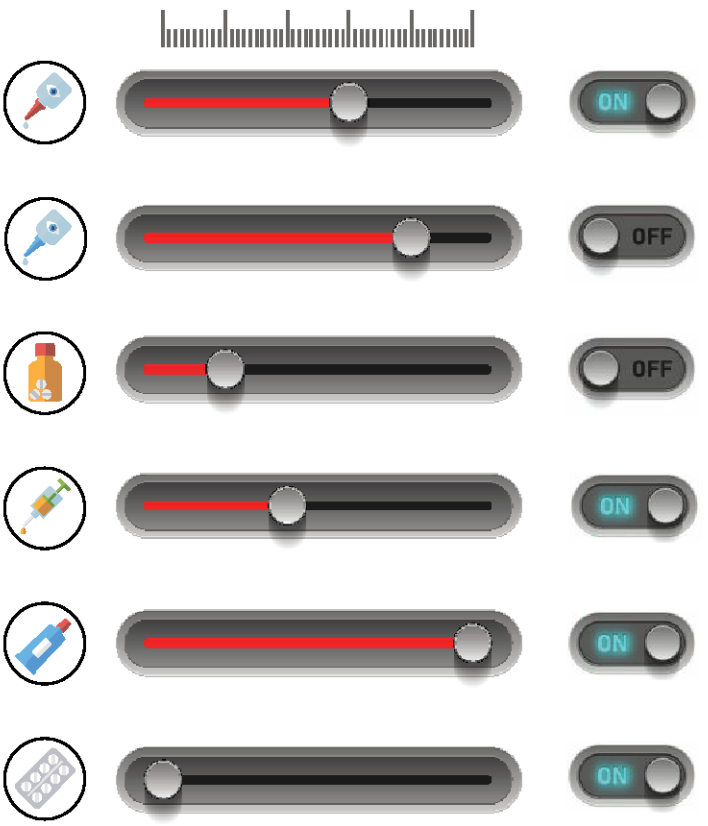

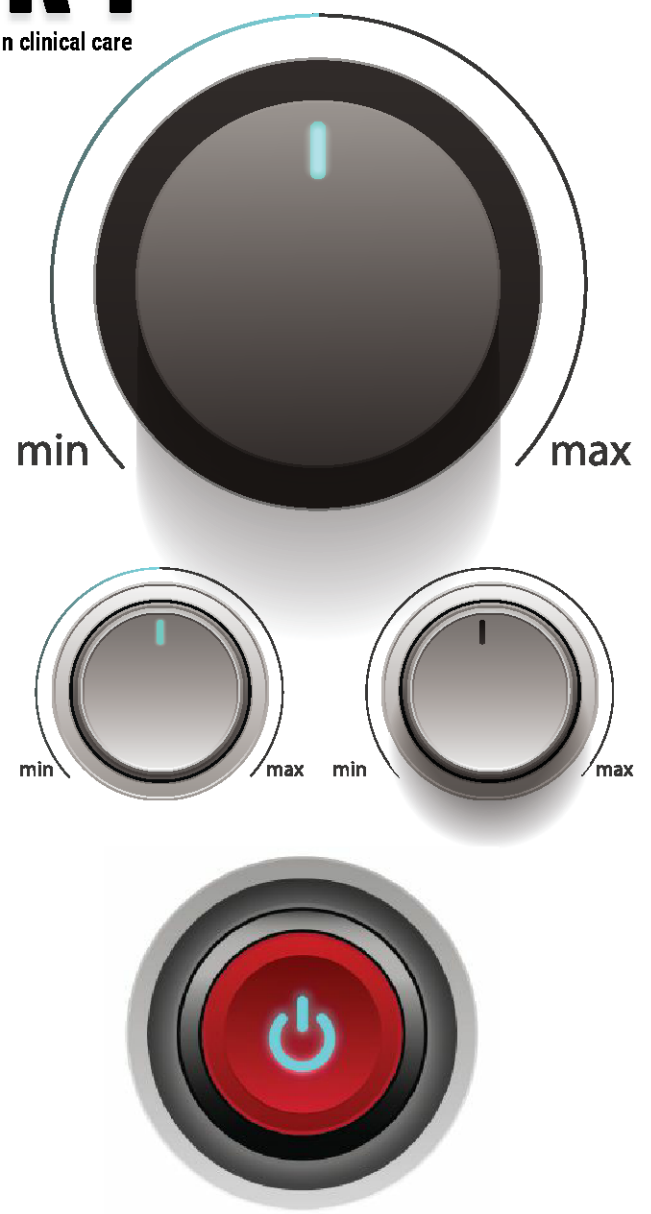

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The contact lens with the
most moisture among leading brands.

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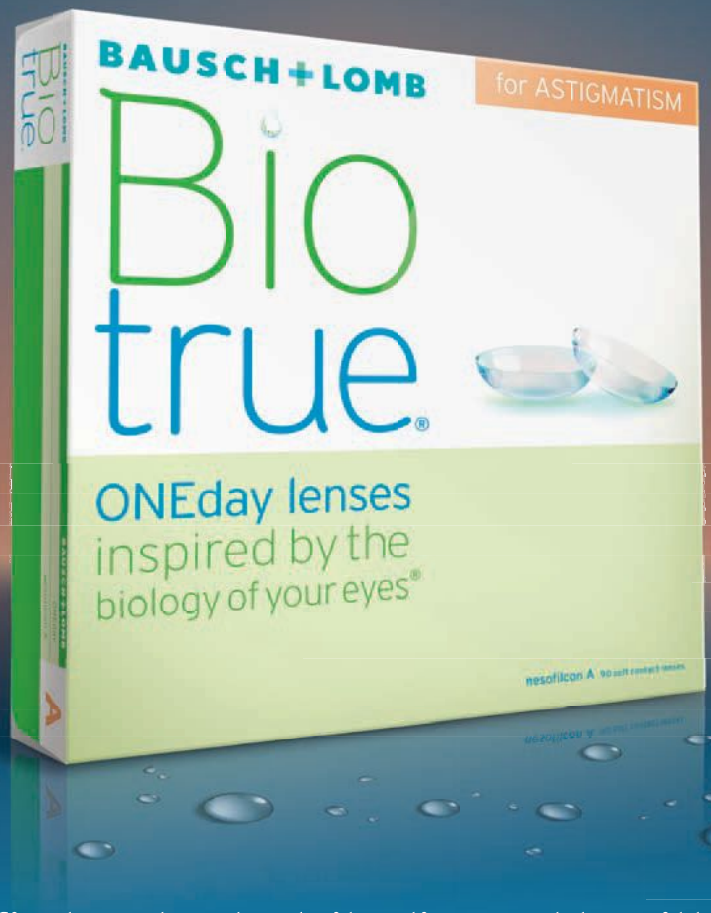
The toric daily disposable with
more parameters than any leading brand.*

ONLY.

The **first and only** daily disposable with
-2.75 Cylinder available as a standard offering.

-2.75 CYLINDER

daily disposable available for **same-day fitting.**



Fit the first and only daily disposable with a -2.75 Cylinder offering—Biotrue® ONEday for Astigmatism.

- **Most moisture** and **toric parameters** among leading daily disposables*
- **Helps reduce halos and glare** with spherical aberration control[1]
- **Fast to fit with excellent centration** at dispensing and follow-up[2]

*Point of sales data from January to June 2021, sourced from third party.

REFERENCES: 1. Results of an online survey with patients who completed an evaluation program for Biotrue® ONEday for Astigmatism contact lenses and wore their trial lenses for ≥4 days (n=1001). **2.** Results from a 7-investigator, multi-site study of Biotrue® ONEday for Astigmatism contact lenses on 123 current non-daily disposable toric soft contact lens wearers. Lenses were worn on a daily wear basis for 1 week.

BAUSCH+LOMB
See better. Live better.

Virginia ODs Can Now Perform Laser Surgery

Similar bills made strides in Colorado and Utah, while Washington state was stymied.

Optometrists practicing in Virginia had reason to cheer earlier this month when, on March 9, Gov. Glenn Youngkin signed identical bills HB 213 and SB 375, which permit the state's ODs to perform three types of laser surgery: capsulotomy, laser peripheral iridotomy (LPI) and selective laser trabeculoplasty (SLT). Virginia is now the eighth state in the country, as well as the biggest, to expand the optometric scope of practice to include these procedures.

Lisa Gontarek, OD, who serves as president of the Virginia Optometric Association (VOA), said that after several years advocating for the bill, seeing all the efforts come to fruition has been encouraging and worthwhile.

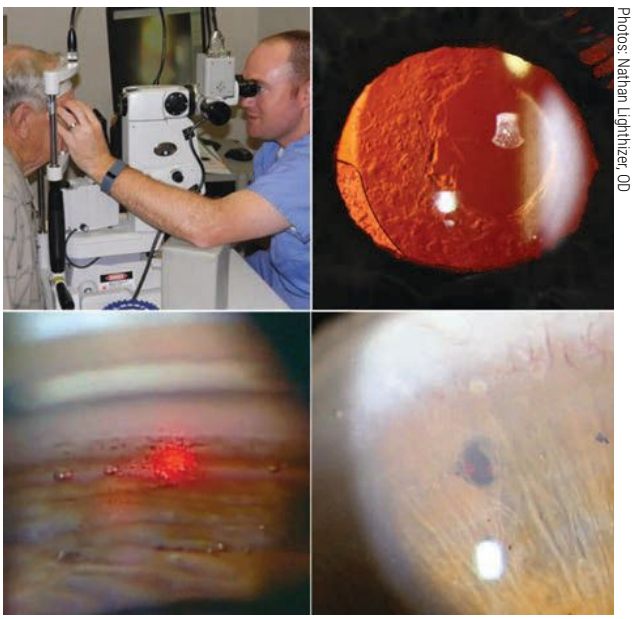
"Everybody has just been really super supportive of it," said Dr. Gontarek. "Immediately after the bill was signed, we received an influx of calls, texts and emails from our members who have been eagerly waiting for this to happen. Optometrists in Virginia are very excited to be able to offer these services to their patients within their clinic, whereas before some patients had to drive hours to receive this type of care."

Dr. Gontarek also points out that the bill's passage gives hope to other states in the process of fighting similar legal battles to expand their optometric scope of practice. "Because we're the biggest state so far that has passed this law, I think that can be very beneficial to other states that are trying to do it," she said. "We're hoping it will be like a snowball effect where other states will start to be successful in their endeavors as well."

The law will go into effect on July 1st. Before then, specific regulations will be developed by the state's board of optometry to ensure every OD in Virginia has the proper training and certification to perform the new procedures. Bo Keeney, executive director of VOA, says that now that the bill has been signed, the process should be finalized fairly quickly.

"We put into the legislation that the education course has to be taught by a college or school of optometry so that there have to be some hands-on and classroom components to the training," said Mr. Keeney. "We're just really happy to see that for the first time, the training and education of today's optometrist is going to be matched with the scope of practice in Virginia."

Dr. Gontarek adds that she's excited about being able to enhance the quality of care she gives to her patients. "I've been seeing some patients in my practice for 15 years, and when I tell them that they're going to need one of these procedures, they ask, 'Can't you just do it for me?' Until now, I've had to say no and send them to someone they've never met," she said. "It will be really nice to have that continuity of care."



Photos: Nathan Lighthizer, OD

A trio of YAG laser procedures is now within the purview of Virginia ODs. The optometry board is currently developing regulations on training and certification.

Utah's Bill Moves Forward

In February, legislation to expand optometric scope of practice in Utah passed the House with a 48-23 vote. The bill, HB224, would allow ODs in the state to perform capsulotomy, SLT and LPI procedures.

"It was a great win for us, accomplished through an impressive grassroots effort by our optometrists," says Weston Barney, OD, president of the Utah Optometric Association. "The bill now moves on to the Senate, where we hope to capitalize on our momentum and continue to educate legislators on the advantages of allowing optometrists to provide these laser treatments as we have been educated and trained to do."

Dr. Barney notes that the legislation is facing strong opposition from local ophthalmology and medical associations. Still, he says he is confident that support and advocacy will continue to grow once legislators recognize the adequate training of ODs in Utah and understand the bill's potential to improve eyecare accessibility across the state.

Scope Expansion Denied in Washington

This past January, legislation was introduced to the Senate regarding scope of practice expansion for optometrists in Washington state. In collaboration with the Senate Health and Long-Term Care Committee, the Optometric Physicians of Washington (OPW) drafted and submitted the proposal, which would have allowed the state's licensed ODs to prescribe oral steroids and remove benign eyelid lesions, as well as perform select laser procedures, including YAG capsulotomy and SLT.

The bill, SB 5542, recently underwent a sunrise review at the state's Department of Health, which Kim Jones, executive director of OPW, notes was mostly favorable to the scope update.

"It received a favorable hearing before the Senate Health and Long-term Care Committee, with a number of OPW members testifying or signing in with support," said Ms. Jones.

Unfortunately, the bill was subsequently voted out of the committee with a 'do pass' recommendation, and on February 17, the Senate ruled it as an X-file, meaning that the bill will not continue to move through the Senate for further consideration.[1]

As discouraging as the news may be to ODs and advocacy groups in Washington, Ms. Jones and other leaders at OPW are not giving up hope. "We will start the process again next year. It is a longer legislative season, and we have learned a lot about challenges in the process and our opposition that will help us in next year's battle," she said.

Colorado Bill Pushes for "As-Taught" Optometry Law

The Colorado Optometric Association (COA) is working to move a bill through its Senate that would sunset and reauthorize the Optometric Practice Act, which would achieve the following major changes in two of its four sections:

(1) continue the board and the regulation of optometry for 11 years, until September 2033, and;

(2) expand the definition of the practice of optometry to include any service, procedure or treatment that falls within the training and skills of the state's optometrists.

A push for "as-taught" legislation such as this is increasingly on the agenda among optometric advocates across the country.

On February 11th, the bill was debated during the first committee hearing in the House Health and Insurance Committee, where several members of the COA testified in its support.

The next committee hearing will be held on March 23 at 1:30pm, where it will be voted on by committee members and determined whether it moves forward. "We expect additional COA members will testify in support at the bill's committee hearing," said Kelli Catlin of the COA. "We anticipate both supportive testimony, opposition testimony and amendments."

Timely updates on the bill, as well as information on the upcoming hearing that can be listened to online, can both be found here: https://leg.colorado.gov/bills/hb22-1233.

Be sure to check our online news feed for updates on this and all other active legislation.

1. SB 5542 - 2021-22 Concerning the practice of optometry. Washington State Legislature. Updated March 11, 2022. Accessed March 11, 2022. https://app.leg.wa.gov/billsummary?BillNumber=5542&Year=2021.

UK Study Affirms Safety of Non-MD Laser Use

Anti-optometry lobbyists often rely on the argument that ophthalmologists are the only medical professional with the necessary training and skill to perform certain ocular procedures, such as laser surgery. This speculation has been disproven time and time again, and another recent study added to the evidence of its falsehood. The results determined that laser procedures such as YAG capsulotomy may be performed safely by other medical professionals, in this case by advanced nurse practitioners, without compromising visual outcomes or effectiveness.

The retrospective consecutive case series included 6,308 eyes of patients who received YAG posterior capsulotomies, 33.1% of which were performed by advanced nurse practitioners and 66.9% of which were performed by ophthalmologists. The median pre-op, post-op and logMAR visual acuity gains were 0.48, 0.18 and 0.30logMAR, respectively. No differences in visual outcomes were detected between patients of either group. There was also no difference in complication rate between operator training levels.

In fact, after adjusting for age, ethnicity, training grade and ocular comorbidities, the nurse practitioners had a significantly lower rate of repeat capsulotomy compared with that of the ophthalmologists. "Younger patients, ocular comorbidities and ophthalmology operators were associated with a higher proportion of those requiring further YAG posterior capsulotomies," the researchers wrote in their study.

The researchers concluded that not only do YAG posterior capsulotomies deliver overwhelmingly positive outcomes, but also, non-ophthalmologists can "safely and effectively contribute to various aspects of ophthalmic healthcare."

Moussa G, Kalogeropoulos D, Ch'ng SW, et al. Comparing outcomes of advanced nurse practitioners to ophthalmologists performing posterior YAG capsulotomy, a six-year study of 6,308 eyes. Eye (Lond). 2022 Feb 28:1-6. Epub ahead of print.

Caffeine Intake Not Linked to Dry Eye

However, higher consumption of this popular pick-me-up was tied to worse symptoms after data was adjusted for comorbidities.

One of the most common complaints optometrists hear from patients in their chairs is "my eyes are dry." Affecting between 5% and 50% of people, dry eye is a multifactorial condition, and as such, research that investigates the various risk factors for this disease is critical and will aid in slowing its increasing prevalence.

A study recently looked into the world's most consumed bioactive substance, caffeine, and its potential correlation to DED. Good news, coffee enthusiasts: the data showed that caffeine intake is not a risk factor for DED in the majority of the population.

Photo: Nathan Dumlao on Unsplash

For the general population, caffeine doesn't seem to increase risk of DED.

The study included 85,302 participants (59% female, average age: 51) who took the Women's Health Study dry eye questionnaire. Caffeine intake was calculated from four commonly consumed beverages: coffee, tea, cola and energy drinks. Other potential sources of caffeine, including chocolate and caffeine pills, were not accounted for in this study.

The average daily caffeine intake was 285mg. The researchers found that after correcting for demographics, body mass index, smoking status and alcohol intake, higher caffeine intake was actually associated with a decreased risk of DED as evaluated by the questionnaire (odds ratio of 0.97 per 100mg/day). The effect was similar between males and females and was not affected by medical comorbidities, reported sleep quality or stress level.

In addition, decaffeinated coffee was found to be associated with an increased risk of DED (OR of 1.05 per cup/day).

The data did show that after adjusting for all comorbidities, increased caffeine intake was linked to highly symptomatic dry eye but a decreased risk of DED diagnosis, which the researchers noted supports the results of previous studies.

"It is possible that caffeine affects dry eye symptoms separately from tear secretion and ocular surface parameters," the researchers wrote in their paper on the study, published in *Cornea*. "Caffeine may also have direct ocular effects and seems to overall stimulate lacrimal gland secretion." They added that because caffeine is a diuretic, some have speculated it may trigger DED through dehydration, but normal consumption has been proven not to have a significant diuretic effect.

Overall, the results of this study support that in the general population, dietary caffeine intake doesn't appear to be associated with DED development, the authors concluded.

Schjerven Magno M, Utheim TP, Kaurstad Morthen M, et al. The relationship between caffeine intake and dry eye disease. Cornea. January 26, 2022. [Epub ahead of print].

IN BRIEF

■ ***Metformin Not Associated with AMD Risk in Diabetes Patients.*** In its late stages, age-related macular degeneration (AMD) is a leading cause of vision loss. Previous studies have suggested that metformin—commonly used to treat diabetes—may be associated with a reduced risk of developing the condition, but the evidence has been inconclusive. **A recent study did not determine a solid association between the medication and the development of AMD.**

The researchers investigated the relationship between metformin use and development of AMD among patients with type 2 diabetes. Their analysis included nearly 174,000 individuals ages 40 and older. The exposed group was prescribed metformin, and the unexposed group was prescribed other antidiabetic medications. The exposure status was treated as time varying, collected at three-month intervals.

No evidence was found between metformin use and development of AMD in type 2 diabetes patients. During follow-up, only 3,111 (1.8%) of patients developed AMD.

Women had a significantly higher risk of developing AMD, as well as those **older in age, current and ex-smokers, and those with high HbA1c levels.**

There was also evidence of a positive correlation between the degree of oxidative stress and glycated hemoglobin, suggesting that **a high HbA1c may accelerate the development of AMD.**

The authors also observed **an association between AMD and sight-threatening retinopathy.** "This could be the result of misclassification or result from the fact the metabolic stress in the retina increases the risk of both AMD and retinopathy—also supported by the association between increased HbA1c and AMD," the authors explained. **"The role of oxidative stress has long been recognized as a hallmark of the disease pathogenesis of AMD."**

The authors suggest **further studies should evaluate whether metformin has an impact on disease progression following a diagnosis of AMD.**

Gokhale KM, Adderley NJ, Subramanian A, et al. Metformin and risk of age-related macular degeneration in individuals with type 2 diabetes: a retrospective cohort study. Br J Ophthalmol. January 20, 2022. [Epub ahead of print].

tyrvaya™
(varenicline solution)
nasal spray 0.03 mg

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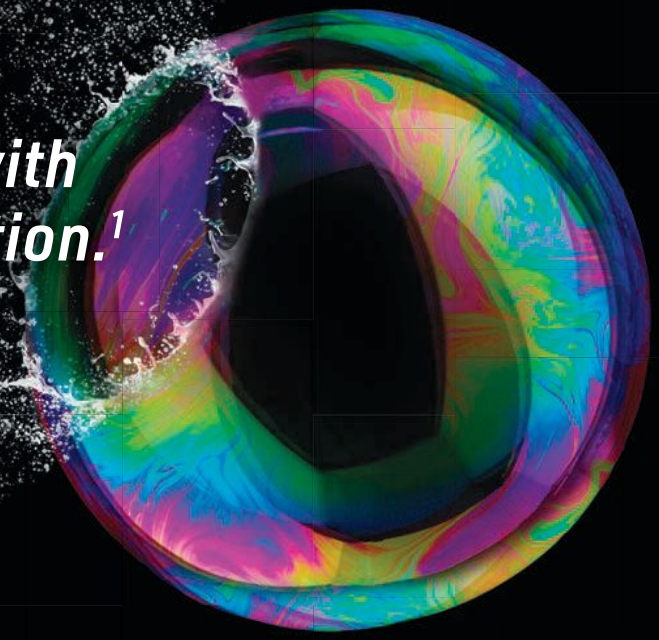


Dry eye starts with tear film disruption.[1]

Treat by activating tear film production.[2]

INTRODUCING A WHOLE NEW WAY TO TREAT DRY EYE DISEASE.[2]

Tyrvaya™, the first and only nasal spray approved to treat the signs and symptoms of dry eye, is believed to activate the trigeminal parasympathetic pathway via the nose, resulting in increased tear film production.[2] The exact mechanism of action is unknown at this time.

Watch Tyrvaya in action at Tyrvaya-pro.com.

INDICATION

Tyrvaya™ (varenicline solution) Nasal Spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Please see Brief Summary of Prescribing Information on the adjacent page and the full Prescribing Information at Tyrvaya-pro.com.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Tyrvaya. Prescribing Information. Oyster Point Pharma; 2021.

IN BRIEF

■ ***Myopia Major Risk for Glaucoma.*** It's long been known that open-angle glaucoma (OAG) risk is higher in patients with high myopia, and recent 10-year study noted that **high myopia was associated with a 7.3-fold increased incidence of OAG** as compared with emmetropic eyes. Average 10-year incidence was 3.0%.

The study reviewed data from 2,695 individuals in the Beijing Eye Study who were re-examined in 10 years' time. OAG was found in 75 participants among 2,494 individuals free of glaucoma at baseline. The 10-year OAG incidence increased from 1.8% in individuals aged 40 to 49 years old to 5.9% in participants ages 70 and over. The study classified refractive status as emmetropia/hyperopia (>-1D), low myopia (≤-1D and >-3 D), moderate myopia (≤-3D and >-6D) and high myopia (≤-6D).

Risk of developing OAG increased by a factor of 1.72 for each 1mm higher axial length. OAG incidence was highest in the high myopia group (13.3%; odds ratio [OR]: 7.3), followed by the moderate myopia group (8.1%; OR: 4.2) and the low myopia group (6.2%; OR: 3.2). OAG also increased by a factor of 1.18 for each 1mm Hg higher IOP at baseline, by a factor of 6.1 for each 1/10 increase in vertical cup-to-disc ratio, in addition to a factor of 1.06 for each year higher in age. It decreased by a factor of 0.98 for each µm thicker central corneal thickness.

The researchers believe their results "should be of importance to clinical protocols and screening strategies," they wrote in their paper.

Wang YX, Yang H, Wei CC, et al. High myopia as risk factor for the 10-year incidence of open-angle glaucoma in the Beijing Eye Study. Br J Ophthalmol. February 22, 2022. [Epub ahead of print].

■ ***CXL Not Needed After SMILE.*** The SMILE refractive surgery procedure has lately risen in stature as a more cornea-sparing alternative to LASIK. Would adding a collagen crosslinking (CXL) treatment after SMILE strengthen the cornea even more? Not really, says a recent study.

A total of 54 eyes of SMILE and 54 eyes of SMILE plus CXL (called SMILE Xtra) patients treated for normal and borderline cases of myopia/myopic astigmatism were included. The authors did not observe a significant difference in the mean regression between the two procedures at almost the same post-op mean follow-up period of 21 months.

The good stability and minimal regression in the SMILE group at the long-term may suggest SMILE itself is a stable procedure in a majority of cases and adding CXL should only be reserved for cases where the risk of ectasia is higher.

Brar S, Sriganesh S, Sute SS, Ganesh S. Comparison of long-term outcomes and refractive stability following SMILE versus SMILE combined with accelerated cross-linking (SMILE XTRA). J Ophthalmol. February 28, 2022. [Epub ahead of print].

Atropine 0.01% Favors Temporal Retina

The renewed interest in myopia control has brought atropine use back into vogue, although optimal dosage recommendations are still being debated and studied. The 0.01% concentration has shown to be safe and effective in halting progression. Researchers recently sought to build on this, specifically looking at the drop's effect on relative peripheral refraction, a quantitative factor in myopic development that measures the difference between central and peripheral visual refraction.

The randomized, double-blinded trial enrolled 73 children split between a study group and a control group. The study group used a placebo for one year followed by six months of atropine 0.01%, while the control group used atropine 0.01% for one year and then switched to placebo drops for six months. Measurements of central and horizontal peripheral refractions (15° and 30° at the temporal and nasal retina) were performed on patients under both non-cycloplegic and cycloplegic states.

The researchers found that under non-cycloplegia, the control group showed significant relative hyperopia in the temporal 30° retina and the nasal retina. In the study group, however, the relative hyperopia in the temporal 30° retina disappeared.

After cycloplegia, the control group had significantly less myopia in central refraction. In addition, the researchers wrote, "As a hyperopic shift in the central refraction, there were significant myopic shifts, which meant less hyperopia in temporal relative peripheral refractions." The study group, however, did not present any significant changes in central refractions or temporal relative peripheral refractions.

The team determined from the data that myopes present more peripheral hyperopia in the nasal retina than the temporal region.

"The curvature of the nasal cornea and the sagittal height of the nasal sclera, which correspond to the imaging in the temporal retina, are both less than the curvature and sagittal height of the temporal part," the researchers explained in their paper. "All these anatomic and physiological properties might work together and promote the nasal-temporal asymmetry of relative peripheral refractions."

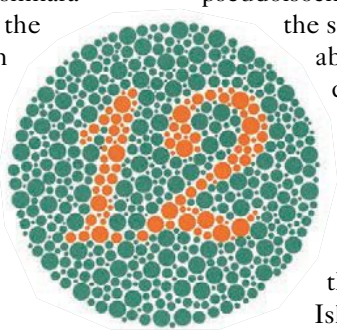
They concluded that, in children with myopia, "Atropine 0.01% eye drops and cycloplegia had more of an effect on temporal relative peripheral refractions." This atropine concentration could alleviate relative hyperopia in the temporal retina and the hyperopic shift before cycloplegia.

Tian J, Wei S, Li S, et al. The effect of atropine 0.01% eye drops on relative peripheral refraction in myopic children. Eye. January 29, 2022. [Epub ahead of print].

Standard Color Vision Test Has Low Sensitivity

Ishihara plates are a staple of optometric practice, despite being known to miss some cases of color deficiency, especially blue-yellow abnormalities. To test their performance in picking up red-green deficiency, researchers recently conducted a cross-sectional study to compare and combine the results from genetic analysis with the Ishihara (24-plate ed., 1964) and the Hardy-Rand-Rittler (4th ed., 2002) pseudoisochromatic plate tests.

The analysis included 454 healthy participants with normal habitual visual acuity. DNA was collected and used in genotyping assays of OPN1LW and OPN1MW genes from each participant, using a test called MassArray.



The Ishihara on its own only detected half of color deficiency cases in this study.

When using pseudoisochromatic plate tests alone, red-green color deficiencies were identified in 5.2% of men and 1.1% of women. Comparatively, the combination of MassArray and pseudoisochromatic plate test results revealed 10.4% of males and 0.8% of females to be color deficient. Combining genotyping with either pseudoisochromatic test "improves the sensitivity considerably, identifying >97% of color-deficient males and misidentifying 1% of color-normal males," the study authors explained in their paper.

Data revealed that the combination of the Ishihara test with MassArray is sufficient in identifying red-green color deficiencies in males, but not females. The researchers determined that including the Hardy-Rand-Rittler test allows for the identification of color deficiencies in females as well as grading of the deficiency.

"In general, even when the genotype is not known, as a minimum, both the Hardy-Rand-Rittler and the Ishihara pseudoisochromatic plate tests should be completed, and the results combined, in the identification of red-green color deficiencies," the researchers concluded.

"Further studies are required to understand the phenotypical implications of cone opsin genes that confer red-green color vision deficiencies that cannot be reliably identified with standard pseudoisochromatic plate tests," they wrote.

Arnegard S, Baraas RC, Neitz J, et al. Limitation of standard pseudoisochromatic plates in identifying colour vision deficiencies when compared with genetic testing. Acta Ophthalmol. February 3, 2022. [Epub ahead of print].

When patients rely on artificial tears alone, inflammation may persist. Xiidra can disrupt the chronic inflammatory cycle in dry eye disease.* It can provide lasting symptom relief in as little as 2 weeks.[1-5†]

*Xiidra blocks LFA-1 on T cells from binding with ICAM-1 that may be overexpressed on the ocular surface in dry eye disease and may prevent formation of an immunologic synapse which, based on in vitro studies, may inhibit T-cell activation, migration of activated T cells to the ocular surface, and reduce cytokine release. The exact mechanism of action of Xiidra in DED is not known.[1,2,5]

† The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle controlled studies (N=2133). Patients were dosed twice daily. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). Effects on symptoms of dry eye disease: a larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf*. 2017;15(3):438-510. **3.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed May 25, 2021. https:/www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628. **5.** Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *J Ocul Pharmacol Ther*. 2017;33(1):5-12.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

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

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

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

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T2020-87

Retinal Photos Help Predict Heart Attack, Mortality

Two artificial intelligence studies show the increasingly vital role fundus assessment plays in systemic health and point toward potential future applications.

The retina offers a unique, accessible 'window' to evaluate underlying pathological processes of systemic vascular and neurological diseases. New research using artificial intelligence (AI) suggests retinal imaging may be capable of identifying patients at high risk for heart attack based on retinal biomarkers associated with cardiac function, such as retinal blood vessel density and tortuosity. A second AI study used retinal photos to determine markers of accelerated aging that might suggest increased mortality risk.

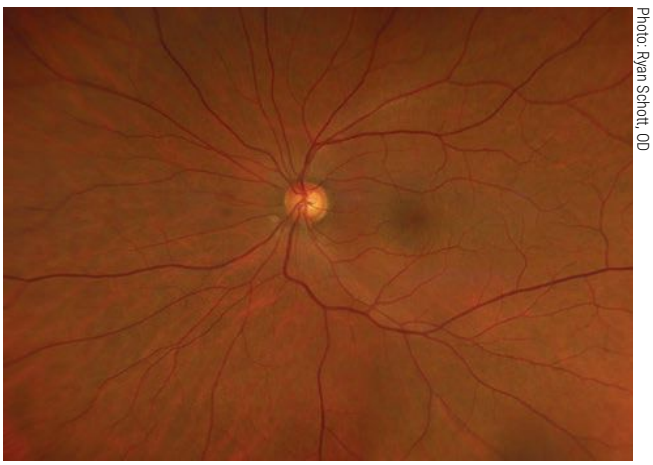

Photo: Ryan Schott, OD

When AI systems are trained on large sets of retinal photos and then paired with data on disease prevalence and mortality data, patterns emerge in that can anticipate health risks.

In the first study, to predict incident myocardial infarction from fundes evaluation, the researchers used a combination of retinal images and patient metadata to estimate left ventricle mass and end-diastolic volume in 5,663 qualifying subjects.[1] Their models employed cardiovascular magnetic resonance imaging (end-diastolic, short-axis view), retinal imaging and demographic data from the UK biobank imaging study.

They found the following, based solely on retinal images and demographic data:

- Mean left ventricle mass was 4.4g.
- Mean left ventricular end-diastolic volume was 3.02ml.
- Risk of myocardial infarction had an area under the curve of 0.8, a sensitivity of 0.74 and a specificity of 0.71.

"Our results indicate that one could identify patients at high risk of future myocardial infarction from retinal imaging available in every optician and eye clinic," the authors wrote in their paper. They noted that using cardiac indices and demographic data together (vs. demographic data alone) can improve prediction of heart attack incidence.

They tested their method on the AREDS dataset as well, reporting a slightly lower performance but an overall discrimination capacity similar to that of established cardiovascular disease risk assessment models. "This highlights the potential for our approach to be employed as a second referral tool in eye clinics/opticians to identify patients at risk of future myocardial infarction events," they noted.

The second study used AI to identify markers of accelerated aging in retinal photos that represent higher risk of mortality. Researchers in China first developed a deep learning model that can predict age from fundus images, known in their study as retinal age. Then, their measure of retinal age gap—the difference between predicted retinal age and chronological age—independently predicted the risk of mortality, especially of non-cardiovascular and non-cancer mortality.[2]

Beginning with a dataset of 80,169 retinal photos, the study used 19,200 fundus images from 11,052 participants without prior medical history at the baseline examination to train and validate the model for age prediction, from which the retinal age was determined. A total of 35,913 of the remaining 35,917 participants had available mortality data and were used to investigate the association between retinal age gap and mortality.

The model achieved a strong correlation (0.81) between retinal age and chronological age, and an overall mean absolute error of 3.55 years. Each one-year increase in the retinal age gap was associated with a 2% increase in risk of all-cause mortality (hazard ratio=1.02), as well as a 3% increase in risk of cause-specific mortality attributable to non-cardiovascular and non-cancer disease (hazard ratio=1.03).

"This risk stratification will assist tailored healthcare decision-making, as well as targeting and monitoring of interventions, the researchers wrote in their paper. "The ability to use fundus images in predicting aging may improve potential health benefits of eye disease screening the health economic cost-effectiveness of programs such as diabetic retinopathy screening, thus increasing the impact and access to eye disease screening programs."

1. Diaz-Pinto A, Ravikumar N, Attar R, et al. Predicting myocardial infarction through retinal scans and minimal personal information. Nature Machine Intelligence. 2022;4:55-61.

2. Zhu Z, Shi D, Guankai P, et al. Retinal age gap as a predictive biomarker for mortality risk. Br J Opthalmol. January 18, 2022. [Epub ahead of print].

Temperature Change Affects Disc Hemorrhage Rates

IOP was also found to be higher in these glaucoma patients during the winter months.

To everything there is a season, and that apparently includes optic disc hemorrhages. Screening for this prominent risk factor in glaucoma is common practice, and if a patient does indeed have a disc hemorrhage, frequent observation helps identify signs of disease progression. Understanding how seasonal variability may impact hemorrhage presentation and corresponding intraocular pressure (IOP) levels will improve diagnostic accuracy. A recent study determined that optic disc hemorrhage varied based on the season; specifically, in relation to the change in monthly average temperatures.

The study evaluated red-free retinal nerve fiber layer photography of patients who had visited the Glaucoma Clinic of Seoul National University Hospital in 2019 or 2020. They gathered data on the monthly incidence rate of disc hemorrhage, patients' IOP levels and seasonal temperature information, which split each 12-month period into three categories based on the recorded monthly averaged temperature:

- <10°C
- between 10°C and 20°C
- ≥20°C

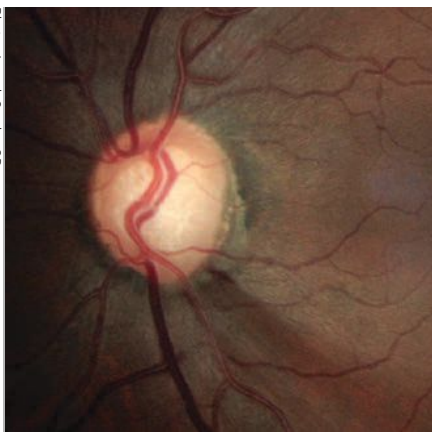

Photo: Joseph Sowka, OD

Decreased ocular blood flow in response to low temperature is one possible mechanism believed to be at work in the clinical findings, researchers say.

Fundus images of 13,707 eyes were obtained for analysis, 454 (3.4%) of which were confirmed to have disc hemorrhage by the two study observers. They determined that as the temperature rose by 1°C, the disc hemorrhage ratio was reduced to 0.1. When they compared the <10°C group to the ≥20°C group, the disc hemorrhage incidence ratio was 1.53.

The researchers also found that IOP levels in hemorrhage patients were higher in winter than in summer. Relative to January, the disc hemorrhage incidence ratio for September, August, July and May was 0.42, 0.54, 0.55 and 0.54, respectively.

"Many studies have reported that increased IOP in the winter is associated with deformation of the lamina cribrosa," the study authors wrote in their paper. "Therefore, it can be considered that incidence of disc hemorrhage increases as IOP increases in the winter season."

The researchers also suggested that this theory may be explained by vascular dysregulation and hemodynamic factors. "It has been reported that a decrease in ocular blood flow in response to a cold stimulus in vascular dysregulation is an indication of a link between endothelial nervous system and autonomic nervous system dysfunction," they noted.

This study concluded that the association between monthly temperature fluctuation and disc hemorrhage incidence may be a topic of interest in further research.

Jang M, Kim YK, Jeoung JW, et al. Analysis of variation in incidence of optic disc hemorrhage according to seasonal and temperature changes. Am J Ophthalmol. February 8, 2022. [Epub ahead of print].

IN BRIEF

■ ***Contact Lens Wearers Understand Importance of Hygiene, Don't Care.*** Knowing might not make all the difference, after all. Researchers in Spain determined that contact lens wearers **admit to failing to replace cases periodically, never replacing their lens cases at all and even using tap water**. However, patient perception of risk associated with some of these bad habits was high. The study believes that efforts should not only increase risk awareness through education but also make follow-through a priority.

The researchers used a self-reported survey to collect demographic and lens wear details, compliance with storage case care and type of received information from their practitioner. The final section involved risk perception, where participants were asked to identify the main consequence of poor compliance with storage case care and to rate from one (no risk) to five (maximum risk) their perception of the risk associated with several non-compliant practices.

The study analyzed 299 completed surveys, with a median age of 24 years (77% females). Most participants were experienced contact lens users, with 30.8% of respondents having used their contact lenses for five to 10 years and 38.1% for more than 10 years. Nevertheless, self-reported compliance with storage case care was poor, with **19% of respondents never cleaning their cases, 69% exposing them to tap water and 26% failing to replace them within six months of acquisition.** Two-thirds of respondents received specific information on case maintenance, but 60% of participants who received written information failed to read it afterwards, which may help explain the actual lack of effect of information on compliance.

However, **perceived risk associated with poor-compliance practices was high** (median values of four and five) and increased with educational level on handwashing and case hygiene, years of lens wear experience and in those patients provided with specific information on contact lens case care.

The study suggested handing a free new storage case to all patients acquiring a bottle of solution as an effective means to improve storage case replacement practices. **"Practitioners may be encouraged to stress to their patients the need to read the information provided to them at home,"** the researchers concluded.

Cardona G, Alonso S, Yela S. Compliance vs. risk awareness with contact lens storage case hygiene and replacement. Optom Vis Sci. February 14, 2022. [Epub ahead of print].

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INDICATIONS AND USAGE

ZERVIATE® (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most commonly reported adverse reactions occurred in approximately 1%-7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

Please see brief summary of Full Prescribing Information on the adjacent page.

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References: 1. ZERVIATE [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals LLC.; 2018. **2.** Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. US Department of Health and Human Services, Food and Drug Administration. Accessed December 29, 2021. https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm. **3.** Meier EJ, Torkildsen GL, Gomes PJ, et al. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. *Clin Ophthalmol.* 2018;12:2617-2628. **4.** Electronic Code of Federal Regulations. Part 349: Ophthalmic drug products for over-the-counter human use. Accessed February 12, 2021. https://www.ecfr.gov/cgi-bin/text-idx?SID=50adb5289f382ac0919186d53a10e0af&mc=true&node=pt21.5.349&rgn=div5#se21.5.349_13. **5.** Malhotra RP, Meier E, Torkildsen G, et al. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. *Clin Ophthalmol.* 2019;13:403-413.

Santen

ZERVIATE® (cetirizine ophthalmic solution) 0.24%

Brief Summary

INDICATIONS AND USAGE

ZERVIATE (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Instill one drop of ZERVIATE in each affected eye twice daily (approximately 8 hours apart). The single-use containers are to be used immediately after opening and can be used to dose both eyes. Discard the single-use container and any remaining contents after administration. The single-use containers should be stored in the original foil pouch until ready to use.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Contamination of Tip and Solution: As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle or tip of the single-use container to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.

Contact Lens Wear: Patients should be advised not to wear a contact lens if their eye is red.

ZERVIATE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.

ADVERSE REACTIONS

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

In 7 clinical trials, patients with allergic conjunctivitis or those at risk of developing allergic conjunctivitis received one drop of either cetirizine (N=511) or vehicle (N=329) in one or both eyes. The most commonly reported adverse reactions occurred in approximately 1%–7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There were no adequate or well-controlled studies with ZERVIATE in pregnant women. Cetirizine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal Data

Cetirizine was not teratogenic in mice, rats, or rabbits at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 1300, 4930, and 7400 times the maximum recommended human ophthalmic dose (MRHOD), on a mg/m^2 basis).

Lactation

Risk Summary

Cetirizine has been reported to be excreted in human breast milk following oral administration. Multiple doses of oral dose cetirizine (10 mg tablets once daily for 10 days) resulted in systemic levels (Mean C_{max} = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean C_{max} = 3.1 ng/mL) following twice daily administration of cetirizine ophthalmic solution 0.24% to both eyes for 1 week. Comparable bioavailability has been found between the tablet and syrup dosage forms. However, it is not known whether the systemic absorption resulting from topical ocular administration of ZERVIATE could produce detectable quantities in human breast milk.

There is no adequate information regarding the effects of cetirizine on breastfed infants, or the effects on milk production to inform risk of ZERVIATE to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERVIATE and any potential adverse effects on the breastfed child from ZERVIATE.

Pediatric Use: The safety and effectiveness of ZERVIATE has been established in pediatric patients two years of age and older. Use of ZERVIATE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIATE in pediatric and adult patients.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

In a 2-year carcinogenicity study in rats, orally administered cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 550 times the MRHOD, on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 220 times the MRHOD, on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 55 times the MRHOD, on a mg/m^2 basis). The clinical significance of these findings during long-term use of cetirizine is not known.

Mutagenesis

Cetirizine was not mutagenic in the Ames test or in an *in vivo* micronucleus test in rats. Cetirizine was not clastogenic in the human lymphocyte assay or the mouse lymphoma assay.

Impairment of Fertility

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 875 times the MRHOD, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION

Risk of Contamination: Advise patients not to touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution. Advise patients to keep the bottle closed when not in use. Advise patients to discard single-use containers after each use.

Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that ZERVIATE should not be used to treat contact lens–related irritation. Advise patients to remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.

Administration: Advise patients that the solution from one single-use container is to be used immediately after opening. Advise patients that the single-use container can be used to dose both eyes. Discard the single-use container and remaining contents immediately after administration.

Storage of Single-use Containers:

Instruct patients to store single-use containers in the original foil pouch until ready to use.

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Drusen Distinguishes Pathways of Intermediate AMD

Multiple risk factors have been identified for age-related macular degeneration (AMD), but pathogenic mechanisms are only partly known. Finding and studying distinct disease pathways within the whole of AMD could facilitate insight into their individual mechanisms. A recent study proposed that there are two distinct disease pathways involving the two major lesions of intermediate AMD: soft drusen beneath the retinal pigmented epithelium (RPE) and subretinal drusenoid deposits (SDD) above the RPE demonstrated *in vivo* by spectral domain OCT. Those with and without SDD had distinct systemic associations, serum and genetic risks—but few in common.

This prospective study was conducted at two tertiary vitreoretinal referral centers in New York City and involved 126 AMD patients. There were 62 SDD (with or without soft drusen) individuals and 64 non-SDD (drusen only) individuals, 51 of whom had cardiovascular disease (CVD) or stroke.

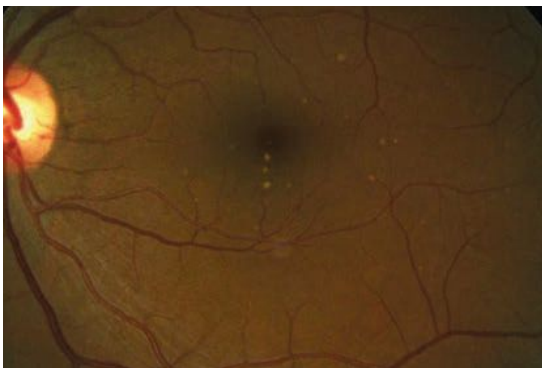

Photo: Bisant Labib, OD

Researchers believe that there may be a pair of separate, often coexisting, diseases that lead to advanced AMD.

SDD was associated with CVD and stroke in 67% of cases, as well as the ARMS2 risk allele and lower high-density lipoprotein (HDL) cholesterol (61mg/dl vs. 69mg/dl), while non-SDD was associated with higher HDL, the CFH risk allele and two lipid risk genes. The 47% of cases of pure SDD (without drusen) further suggest SDD is a distinct retinal pathology. Damage from SDD could then lead, along with that of soft drusen, to advanced AMD.

"What we have shown, specifically, is that patients with SDD, with or without drusen, differ significantly from non-SDD eyes in AMD in their associations with CVD and stroke, serum risks and genetic risks, consistent with the concept of distinct disease pathways," the researchers wrote. "This is not proof of different cause and effect, but the growing mass of such differences, without a single significant unifying observation to balance it, is striking."

The study authors noted that they believe that research on the mechanisms of AMD could be guided by studying the risks that apply specifically to only one or the other pathway. "These distinctions could enable focused attention on specific risks and single pathways, with correspondingly higher chances of success, they concluded. "The specific association of cardiovascular disease and stroke with SDD in particular merits further study."

Thomson RJ, CHazaro J, Otero-Marquez O, et al. Subretinal drusenoid deposits and soft drusen: are they markers for distinct retinal diseases? Retina. February 23, 2022. [Epub ahead of print].

Higher IOP Tied to Sex, Age and Corneal Thickness

Researchers involved in the Laser in Glaucoma and Ocular Hypertension Trial's (LiGHT) sister study, LiGHT China, recently reported that its cohort's baseline higher intraocular pressure (IOP) was correlated to younger age, male sex, greater central corneal thickness (CCT) for primary open-angle glaucoma (POAG) patients, whereas only greater CCT seems to be a risk factor in patients with ocular hypertension (OHT). They also noted that IOP of glaucomatous or OHT eyes varies and reaches peak value mostly at early morning or late afternoon and the trough value at early afternoon.

The prospective randomized trial included 622 glaucoma and 149 OHT patients who underwent Goldmann tonometry at five intervals throughout the day. Mean baseline IOP was 20.2mm Hg for POAG patients and 24.4mm Hg for OHT patients. Greater CCT was correlated with higher IOP in both, while male sex and younger age correlated with higher IOP in the glaucoma group only.

"The role of age and its relationship with IOP still remains controversial," the researchers noted in their report. "Numerous studies have shown a positive association between older age and higher IOP. However, our study revealed a negative correlation between age and IOP in POAG patients, consistent with findings of others in Asian populations."

IOP reached a peak in the morning at 8am and decreased during the day, with a trough at 2:30pm. Mean IOP fluctuation was 3.4mm Hg in POAG and 4.4mm Hg in OHT eyes.

An interesting finding: in both POAG and OHT eyes, the right eyes were more myopic than the left. They concluded, "this confirmed that right eyes have longer axial length than left eyes."

Yang Y, Zhang X, Chen Z, et al. Intraocular pressure and diurnal fluctuation of open-angle glaucoma and ocular hypertension: a baseline report from the LiGHT China trial cohort. Br J Opthalmol. January 27, 2022. [Epub ahead of print].

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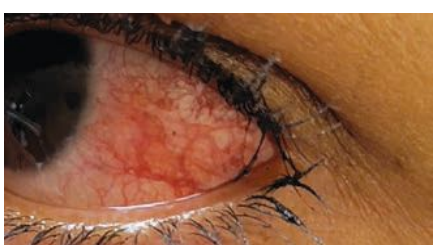

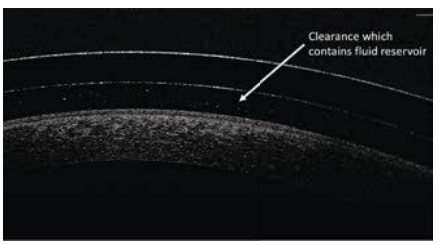

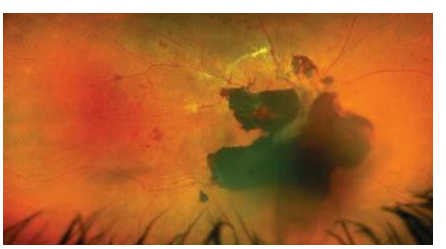

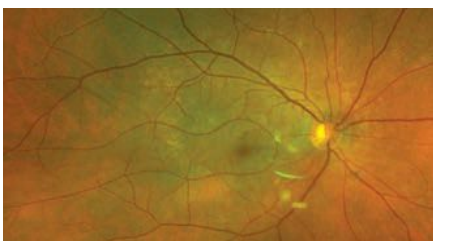

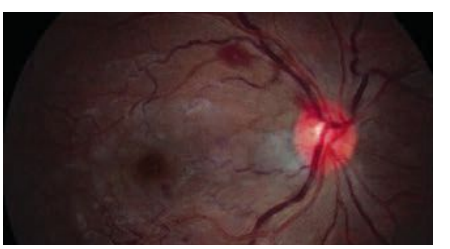

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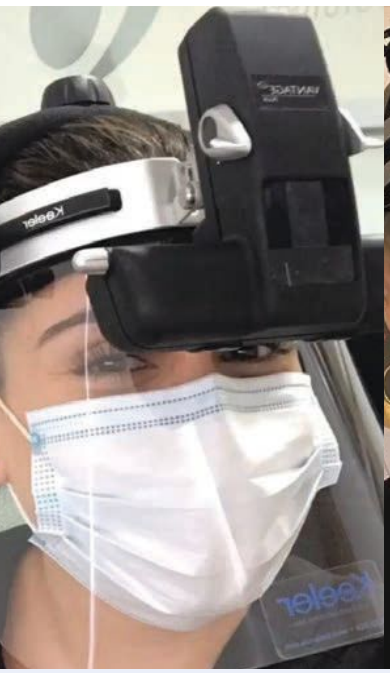

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BY JACK PERSICO
EDITOR-IN-CHIEF
OUTLOOK

You May Fire When Ready

Virginia's new laser law offers optometrists an important new opportunity—and a test.

One of the big topics of discussion at SECO earlier this month—aside from the palpable feeling that the pandemic's worst effects on social interaction had finally abated—was the news that broke during the conference that Virginia's scope expansion law had passed. Come July 1, properly trained ODs in the state will be able to perform three YAG laser procedures: posterior capsulotomy, laser peripheral iridotomy and SLT.

This is a big win for optometry at a critical time, as several other states have similar bills in the offing right now. "Because we're the biggest state so far that has passed this law, I think that can be very beneficial to other states that are trying to do it," said Virginia Optometric Association President Lisa Gontarek, OD, in our news story on the legislation. "We're hoping it will be like a snowball effect where other states will start to be successful in their endeavors as well."

Virginia is the US's 12th most populous state. Its population of 8.6 million is nearly twice that of Louisiana, previously the largest state with a laser law on the books. And with just over 1,000 practicing optometrists, Virginia also contains twice as many ODs as the previous top laser-approved state by optometric licenses (Kentucky).

It's clear that laser laws will be to this decade what diagnostic and therapeutic laws were to previous eras: a defining battleground where ophthalmology and optometry spar, often pointlessly. As has been said time and again, optometric scope expansion helps ophthalmologists too, relieving their backlog of cases so they can concentrate on high-level procedures.

When you hear cries of professional overreach, bear in mind that scope battles arise largely because of structural inertia within organized medicine. Nature abhors a vacuum, as they say, and ophthalmology created one in its workforce capacity. There simply aren't enough ophthalmologists practicing now to meet demand for eye care and far too few MDs in ophthalmology residency programs to fill the gap.

So, enter optometry—through a door ophthalmology left wide open.

Virginia's case and the general disposition of efforts elsewhere represent the culmination of years, sometimes decades, of tireless advocacy outlining the advantages of optometric care. Now comes the time to deliver on those promises. The one area where opponents have a chance to gain a toehold is their argument that some previous scope advancements have gone begging as local ODs failed to take advantage of their newfound laws.

No one should feel compelled to adopt a procedure they don't want to add to their practice—there are many valid reasons to take a pass on lasers, if you so choose—but we need to see enough uptake (and demonstrable improvement in the lives of patients) to justify the effort and keep the momentum going. There's a reason these are called laser *privileges*. Fortunately, the rollout looks to involve teaching institutions and other stakeholders that have optometry's back. This magazine does too, and we'll be launching a new series shortly that aims to share laser expertise with motivated newcomers.

For now, celebrate. Then get to work. We'll be with you every step of the way! ■

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BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

The Power of the Pen

Keep in mind these newer meds when writing prescriptions.

Optometry dominates in ophthalmic drug prescribing, as is evident by the fact that only 18% of prescriptions for Vuity (pilocarpine 1.25%, Allergan)—the new presbyopia eye drop—have come from ophthalmologists. It's not as uncommon as you might think. Xiidra (lifitegrast ophthalmic solution 5%, Novartis) prescriptions for dry eye disease have been written from more than two-thirds of optometrists and almost all topical ophthalmic agents approved in the last few years have more prescriptions from optometrists as well. Let's look at conditions where the power of the pen can be applied.

Glaucoma

Recent years have seen a new class of medications (the ROCK inhibitors Rhopressa and Rocklatan, both by Aerie), a prostaglandin analog (Vyzulta; Bausch + Lomb) with nitric oxide-releasing technology and a new focus on sparing the ocular surface. ROCK inhibitors have significant IOP reduction capability and make an ideal second-line treatment in either moving a patient on prostaglandin analogs to Rocklatan or replacing them with Rhopressa. Vyzulta, with its nitric oxide release, delivers additional IOP lowering of more than 2mm Hg in 42% of patients, more than 3mm Hg in 30% and 5mm Hg in 12% compared to latanoprost.

With more states allowing optometrists to perform laser procedures, we can greatly assist our glaucoma patients with selective laser trabeculoplasty as a first-line treatment. Durysta (Allergan), a new sustained-release delivery system, provides a slow release of bimatoprost once the device is placed in the anterior chamber. What's most impressive is that it dissolves in about three months, but most patients see 18 to 24 months of IOP lowering effect, equivalent to dosing topical bimatoprost QHS.

> **Almost all topical ophthalmic agents approved in the last three to five years have more prescriptions from optometrists.**

Dry Eye Disease

Patients with significant staining are best treated with short-term steroids, such as Eysuvis (Kala Pharmaceuticals) on-label or Lotemax SM (Bausch + Lomb) off-label, and then saving them for future flare-ups. Cyclosporine and lifitegrast are good long-term inflammation treatments, as well as omega fatty acids. But you have to treat the cause, and for most dry eye that's blepharitis—either MGD, *Demodex*, bacterial or a mixture.

A new lipid-solubilizing topical pharmaceutical that targets MGD may be available soon—NOV03 (Bausch + Lomb.) It notably achieved sign and symptom endpoints in only two FDA pivotal trials.

TP-03 (Tarsus) recently completed its Phase III pivotal trial to treat *Demodex* blepharitis. If the data comes anywhere near the success of the first Phase III trial, we'll have our first therapy for eradication of the *Demodex* mite in 2023.

Presbyopia

Vuity extends depth of focus via a miotic pupil with 1.25% pilocarpine. This small-pupil effect peaks at one hour and slowly diminishes over the next three to six hours. The drop's formulation is such that, once placed in the eye, it allows the pH to quickly move to the physiological range, which should decrease burning and stinging side effects. Other common side effects include headache or browache, redness and dimming of vision.

Ideal patients appear to be those who have presbyopia but not necessarily early presbyopia, where they can still accommodate somewhat well. Be cautious of patients with a history of uveitis, cystoid macular edema or high myopia, and retinal conditions such as vitreomacular traction syndrome or retinal thinning, holes, tears or a history of a retinal detachments.

Oral Medications

Don't forget about these, as all but two states have recognized that systemic meds for ocular indications are essential to optometry's role. Low-dose doxycycline or azithromycin is helpful for conditions ranging from blepharitis to ocular rosacea and even recurrent corneal erosion. Hordeola, preseptal cellulitis and non-responsive bacterial conjunctivitis require medications like Keflex (Advancis Pharmaceutical) or Augmentin (GSK). Oral steroids such as Medrol Dosepak (Pfizer) can help with severe allergies around the eye, and Evoxac (cevimeline) can benefit Sjögren's syndrome patients.

Armed with this information, prescribing these therapeutics will greatly help your patients achieve successful outcomes for their ocular conditions. ■

About Dr. Karpecki **Dr. Karpecki** is the director of Cornea and External Disease for Kentucky Eye Institute, associate professor at KYCO and medical director for Keplr Vision and the Dry Eye Institutes of Kentucky and Indiana. He is also chair of the New Technologies & Treatments conferences. He consults for a wide array of ophthalmic clients, including ones discussed in this article. Dr. Karpecki's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

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BY MONTGOMERY VICKERS, OD

CHAIRSIDE

Keep Calm and Carry On

COVID is a real threat, but so is the fear and stress it brought.

I write because I have the time. My first three patients this afternoon all called in with COVID. This has happened a little too frequently lately. Seems like when the day is sunny and beautiful, that somehow triggers COVID. Never happens on a yucky weather afternoon. Has that been studied? If you see Fauci, could you run that by him, please?

Me? I have been in denial. I respect but do not fear COVID. I mean yes, I am vaccinated and I wear a mask when I should, when with the staff or patients or when I am asked to by a business. I wash my hands as I have done between every patient over the past 42 years. Of course, now I wash my hands in front of the patient. They seem to like it. I just assume they are singing "Happy Birthday" twice while they watch.

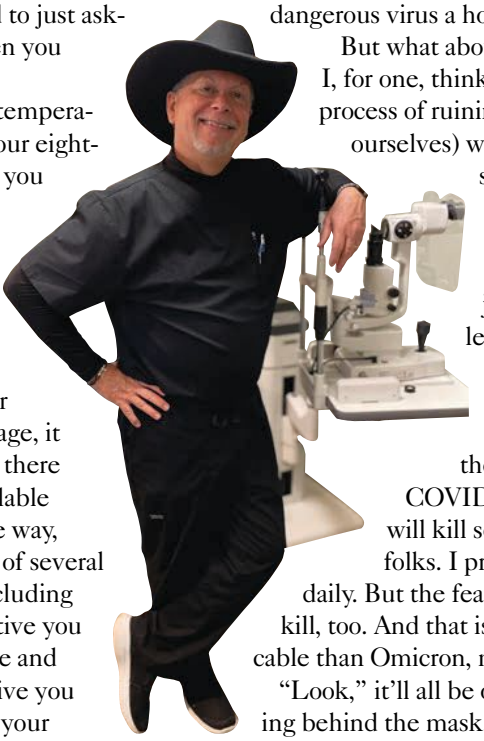
And, I have only shook hands with someone probably two times in the past two years. Sorry, I know some of you think I should chop my hands off at the wrist after such a terrible act. But when an 82-year-old World War II veteran who fought at Normandy reaches his hand out, I am shaking it. Or a five-year-old soccer player. It's how I was raised. I am not afraid they'll kill me.

The staff's response to COVID seems to be one of paranoia. Geez. A contact lens rep came in and coughed through their mask. Two of my employees ran outside to hide—I mean, to smoke. Everyone knows that cigarettes are safer than somebody wearing a mask who is vaccinated coughing 30 feet from you. And they think they should go into quarantine for a week every time they hear a politician say, "Look," before lying about something. During the Clinton era, that was just a drinking game.

Supplements are all the rage, admit it. You take vitamin C, right? No? Liar, you know you do. And on top of that, enough zinc to galvanize your liver, CBD for depression and MCT oil for your COVID-induced 20 pounds. Don't forget the probiotics for your MCT-induced diarrhea. Diarrhea? Better go get tested for COVID.

There are lines around every street corner for people to get tested. Should you stand shoulder to shoulder with every hacking person in town to get tested for something that you catch when you stand shoulder to shoulder with every hacking person in town? Whatever happened to just asking for a day off when you need it?

But if you have a temperature or can't smell your eight-year-old son's socks, you might be sick. Just stay home. Don't wander into every clinic to get tested unless you feel it's going to get way worse, which for many of us at this stage, it will not. No wonder there are shortages in available tests. Oh, and by the way, the CDC assures us of several important truths, including that if you test negative you could still be positive and that if you test positive you have already spread your lovely aerosols to everyone around you anyway.



And, in case you didn't hear the latest, you should definitely mask up, but it's not clear that masks even prevent transmission in the first place.

By now, many of you are mad at me. You think I am making light of a virus that can have devastating effects. I am not. I know that COVID can lead to very serious illness and death. That's not funny.

What is funny is that nobody will tell us how many people in the hospital are there with COVID and how many are there because of COVID. They test everyone who comes in, even if they are there for an ingrown toenail. Also, the majority of folks in the hospital are not well to begin with. Oddly enough, they are not all there for the cafeteria food. I know, I was surprised to learn this, too. Many patients entering a hospital setting have very terrible comorbidities that can make an already dangerous virus a horrifying risk.

But what about the rest of us? I, for one, think we are in the process of ruining our kids (and ourselves) with a level of stress that could have been at least attenuated a bit if we had all just taken a collective deep breath (through our N95s of course) before hiding in the attic.

COVID has killed and will kill some wonderful folks. I pray about that daily. But the fear of COVID can kill, too. And that is more communicable than Omicron, my friends.

"Look," it'll all be okay. Keep smiling behind the mask. ■

About Dr. Vickers

Dr. Vickers received his optometry degree from the Pennsylvania College of Optometry in 1979 and was clinical director at Vision Associates in St. Albans, WV, for 36 years. He is now in private practice in Dallas, where he continues to practice full-scope optometry. He has no financial interests to disclose.

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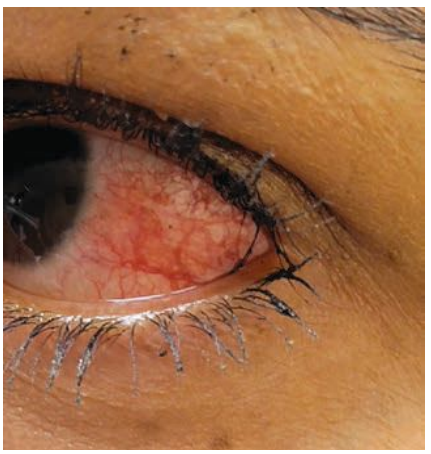
Suspicious Sector

When confronted with this distinctive pattern of injection, episcleritis isn't always the correct diagnosis.

Q A patient presents for a second opinion after being diagnosed with episcleritis three weeks ago and unresponsive to topical steroids. What are some other differentials to think about?

A "Despite being the first diagnosis, is episcleritis the correct diagnosis?" asks Mahsa Masoudi, OD, an ocular disease resident at Omni Eye Services of Atlanta. When faced with the presentation of sectoral bulbar conjunctival injection, most clinicians rush to judgment with a diagnosis of episcleritis.



Don't jump to conclusions when faced with sectoral injection.

Explore Your Options

Take a moment, rather, and consider other possibilities. Lids and lashes can be causative offenders when considering secondary sectoral redness due to possible ingrown lashes, floppy eyelid syndrome, canaliculitis or *Staph*-related toxicity or hypersensitivity.[1] Marginal corneal ulcers and infiltrates erupt in smaller patches of sectoral injection proximal to the cornea as well.

Beyond episcleritis, other conjunctival differentials a clinician must consider include pingueculitis, inflamed pterygium, phlyctenulosis, subconjunctival hemorrhage and conjunctival abrasion.[2] Also keep in mind obvious and occult foreign bodies and trauma. Always start with a good case history to rule out several of these differentials. History includes not only a patient's ocular and medical status but their social and hygiene habits as well.

"Sometimes you have to dig for information and repeat your questioning in different ways," Dr. Masoudi says. "A patient we saw recently adamantly denied trauma, but, on repeat questioning, 'remembered' that a branch whacked him in the eye while doing yardwork a day earlier, she says. Dr. Masoudi advises that following a comprehensive case history, a thorough slit lamp exam and fluorescein will often tell you the rest."

In this case, the patient's long, mascara-coated lashes pointed straight to the answer with fluorescein lighting up the conjunctival runaway. Repetitive mechanical trauma from her lashes alone led to a significant temporal conjunctival abrasion.

A little fluorescein goes a long way. If you think about a conjunctival abrasion first and confirm it with fluorescein staining, then you can go right to an antibiotic rather than using a steroid that will only delay proper healing.

Removing the offending agent, followed by treatment with a topical antibiotic four times a day for one week, helped totally resolve the issue. Epilating the particular misdirected lashes and educating our patient on the effects of less eye makeup and more lid hygiene will hopefully help prevent this from happening again.

Bottom Line

When you see sectoral injection, think conjunctival abrasion until proven otherwise! Once you rule that out, hone in on the other differentials, including episcleritis. Mild cases can resolve on their own or may require a steroid. More advanced simple or nodular episcleritis cases may be accompanied by pain and a systemic history, so think about a workup, especially if episodes are recurrent.

Lab testing should include antinuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), fluorescent treponemal antibody absorption (FTA-ABS), microhemagglutination-*Treponema* pallidum (MHA-TP), rapid plasma reagin (RPR), serum uric acid and a chest X-ray.[4] Consider more aggressive topical therapy along with oral NSAIDs as you comanage these cases with rheumatology.

In the end, Dr. Masoudi reminds us, "though episcleritis is not rare, it certainly is not very common either, so first consider conjunctival abrasion when confronted with sector injection." ■

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About Dr. Ajamian

Dr. Ajamian is the center director of Omni Eye Services of Atlanta. He currently serves as general chairman of the education committee for SECO International and is vice president of the Georgia State Board of Optometry. He has no financial interests to disclose.

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BY BISANT A. LABIB, OD

All Squared Away

While often overlooked, the Amsler grid can help distinguish macular diseases from other ocular conditions.

The macula is one of the most important ocular structures and is an essential part of any funduscopic examination. It is located approximately 3mm, or two disc-diameters, temporal to the optic nerve head and houses the fovea at its center. One of its many unique properties is that the macula contains the highest density of rod and cone photoreceptors, resulting in the sharpest visual acuity in this region.[1]

This delicate area is sensitive to change and can often be difficult to examine. Ancillary testing and a thorough patient history can help distinguish macular diseases from other types of ocular disorders. A simple and often overlooked test that can aid in these situations is the Amsler grid.

Background

Named after Marc Amsler, a Swiss ophthalmologist active in the 1940s, the Amsler grid is a 10cm-by-10cm box that contains a series of smaller squares.[1-4] Each square within the grid subtends an angle of approximately 1°.[4] When viewed centrally at a testing distance of 33cm, it maps the central 10° field corresponding to the macula.[1]

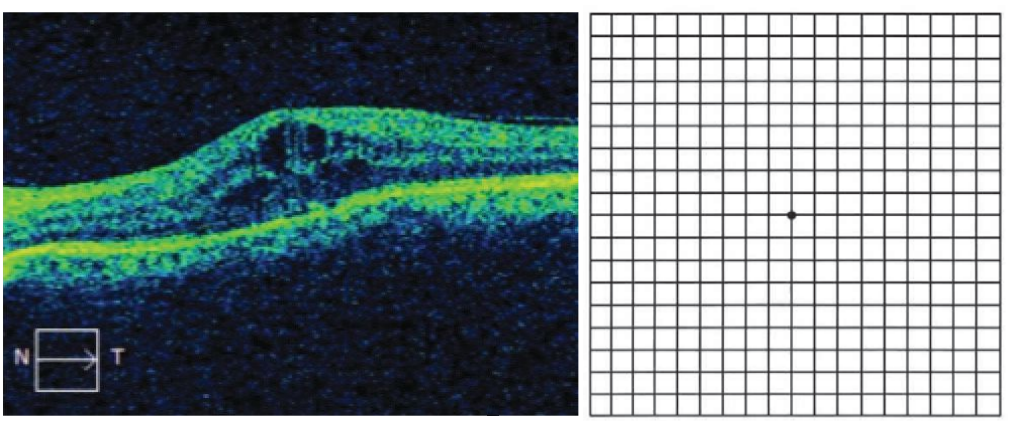
Amsler grid testing is typically performed monocularly with best near vision correction in place and undilated with adequate and uniform illumination over the grid. The patient is then asked to fixate on the central dot and should simultaneously be able to view all four corners of the grid. Failure to do so could indicate peripheral field loss of a non-macular origin.

Afterwards, ask the patient to note if any areas or boxes within the grid appear wavy, distorted, dim or broken. If so, it is a good idea to have the patient draw the abnormality, both to help identify the pathological area as it corresponds to the macula and to monitor the status or progression of the defect over time.[1]

A positive test indicates that the patient is experiencing either metamorphopsia or a scotoma, both of which indicate an underlying macular disease origin. Metamorphopsia is the distortion of an object, whether that be in size, shape or other kind of appearance. In the initial manifestation of metamorphopsia, patients may perceive an "instability" in their vision, rather than true distortion.[1]

There are two variations of metamorphopsia: micropsia and macropsia. In micropsia the parallel lines in the grid appear closer together, whereas in macropsia the lines are distorted further and curved away from each other. Micropsia is more common, and patients may perceive that an object or image is smaller than it appears vs. larger in macropsia. It has been suggested that when retinal elements are displaced in closer proximity to one another, this manifests as macropsia. In a similar manner, a condition such as macular edema where fluid elevates and displaces the photoreceptors away from each other would cause micropsia.[1,4]

Recent evidence suggests metamorphopsia is due to a combination of cortical and retinal changes. Originally, it was thought that metamorphopsia arose purely from the structural changes that occur within the outer retinal layers—mainly photoreceptors—affected in macular disease, ultimately leading to impaired light signal transduction. This is evident in cases such as cystoid macular edema. Recent literature, however, suggests that inner retinal changes and cortical processing are both contributory to the phenomenon.



Cystoid macular edema (left), which would manifest as central metamorphopsia on Amsler grid (right).

About Dr. Labib

Dr. Labib graduated from Pennsylvania College of Optometry, where she now works as an associate professor. She completed her residency in primary care/ocular disease and is a fellow of the American Academy of Optometry and a diplomate in the Comprehensive Eye Care section. She has no financial interests to disclose.

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INDICATIONS AND USAGE

CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

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

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

Please see brief summary of Full Prescribing Information on the following page.

References: 1. US Patent 9,937,225 B2. **2.** Cholkar K, Patel A, Vadlapudi AD, Mitra AK. Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. *Recent Pat Nanomed.* 2012;2(2):82-95. **3.** Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.

PM-US-CQA-0831 08/2021

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CONTRAINDICATIONS

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ADVERSE REACTIONS

Clinical Trials Experience

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

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data

Animal Data

Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation

Risk Summary

Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use

The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Handling the Vial

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

Use with Contact Lenses

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

Administration

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

Rx Only

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PLR-00020 2018

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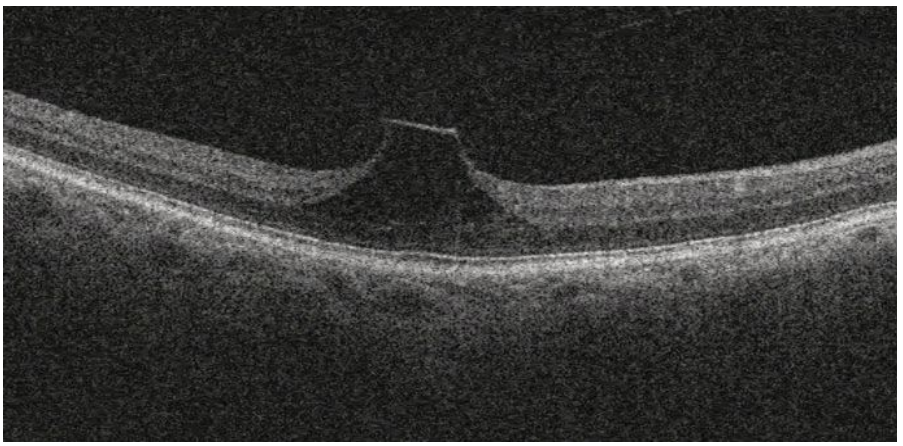

This patient has vitreomacular traction and is monitoring symptoms of metamorphopsia with at-home Amsler grid testing.

In cases of epiretinal membrane formation, thickening of the inner retinal layers correlates highly with metamorphopsia. This is possibly due to the presence of Müller, amacrine, horizontal and bipolar cells within these layers that are disrupted, leading to impaired synaptic function within the photoreceptors. In cases of persistent maculopathy or following treatment of neovascular age-related macular degeneration (AMD), metamorphopsia is not only caused by displacement of light onto the retina but also by changes in cortical processing.[4]

A scotoma is the absence of a spot on the visual field, which can either be absolute or relative. In an absolute scotoma, the missing area is present regardless of any variation in stimuli. In contrast, relative scotomas in the visual field can become more visible with increases in stimuli. The Amsler grid test is more useful in identifying absolute scotomas, where a patient perceives a broken box or missing line. An underlying macular condition that would yield this type of result is a macular hole.[1]

Pros and Cons

Amsler grid testing offers several advantages. Its chief utility is that it is cost-effective and can be efficiently administered chairside. It is also readily available and can be sent home with the patient for self-monitoring. This testing does not require a great deal of patient training due to its ease of use.[2] Oftentimes, a patient may subjectively report metamorphopsia in the setting of absent or very subtle funduscopic signs when standard visual acuity measurements are normal.[4] In such cases, an abnormality on Amsler grid testing would indicate need for a more careful examination or follow-up.

It is well documented that the Amsler grid is optimal for ocular diseases confined to the macula. These conditions include, but are not limited to, wet or neovascular AMD, central serous chorioretinopathy, epiretinal membranes, cystoid macular edema and hydroxychloroquine-associated macular toxicity.[1]

Also of note, this test can be effective in detecting field defects secondary to glaucoma. In a study investigating the efficacy of Amsler grid testing among patients with advanced glaucoma in Ethiopia, the black-on-white grid resulted in a sensitivity of 80.4% and a specificity of 95.4%. The study concluded that the Amsler grid can be used as an effective screening tool in areas where a Humphrey visual field perimeter is not readily available and in the detection of glaucomatous visual field defects that affect the macula.[2]

While this test offers many advantages, it lacks the ability to properly test patients with loss of central fixation commonly documented in those with macular disease, which particularly affects the fovea.[3] Patients with significant central loss have a difficult time with test administration due to their inability to locate the central fixation point.

Additionally, a compensatory "filling in" mechanism that is a normal function of visual perception can alter test results. This is called the cortical completion phenomenon. A common example of this phenomenon is the eye's blind spot. Even in a normal eye, there is an absence of photoreceptors in this unique anatomical region. However, we do not perceive this area as "blind" or absent in our visual field because of a cortical mechanism that fills this area with a similar appearance to its surrounding environment. As a result, our perception is that it is not absent visual space.[5] In this manner, a patient undergoing Amsler testing can have a similar compensatory mechanism and be unable to distinguish a small scotoma from the surrounding area, making the test results of little to no clinical value.

Takeaways

As with all clinical tests, the Amsler grid offers a unique variety of benefits that aid in the diagnosis and management of ocular disease, particularly retinal disorders. However, it is not without its disadvantages. As such, it should be used in conjunction with a full history and ophthalmic examination. Understanding the test procedure, anatomical correlations and interpretation of results is necessary in using the Amsler grid to its fullest potential. ■

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Light Therapy in Managing Meibomian Gland Dysfunction

By Laura M Periman, MD and Sathi Maiti, OD

For many years, the application of a warm, wet wash cloth over the eyes for several minutes, a few times per day over the course of several weeks (if not indefinitely) was the common recommendation to patients with meibomian gland dysfunction (MGD).[1] The general consensus among clinicians, however, was that the lack of standardization in heating tools, and duration and frequency of application might have resulted in inconsistent results and, therefore, poor patient adherence to recommended therapy.[1]

MGD is present in as much as 86% of dry eye patients and is associated with a change in the quality and quantity of the oil secretions from the meibomian glands.[2] Screening for these patients can be as simple as a slit-lamp examination of the lid margins and evaluation of the meibomian gland oil quality and expressibility with applied pressure. Some practices use tear film interferometry to confirm a reduction in tear film oils or meibomian gland imaging to confirm ghosting, truncation and/or atrophy.[3]

If meibomian gland architecture appears present on meibomian gland imaging but gland diagnostic expression provides little yield, there might be blockage in the glands. Heat therapy is recommended for these patients because the melting point of the abnormal meibum with MGD is nearly 4°C higher compared to healthy meibum (Table 1).[4]

Table 1. Comparison of characteristics of patients with and without meibomian gland dysfunction (MGD).

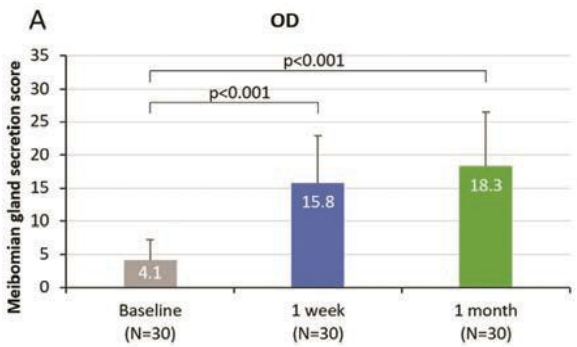
	Normal (°C)	MGD (°C)
Meibum Melting Point[4]	28.9	32.2
Eyelid Temperature[5]		
Upper Eyelid	34.3	34.3
Lower Eyelid	32.4	32.7
Optimum Therapeutic Temperature[6]	40.0	41.5

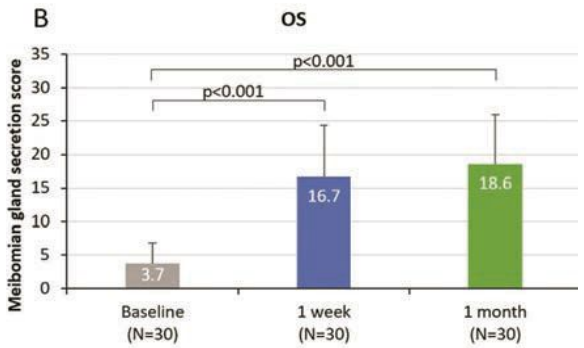
To make matters worse, the average temperature of the tarsal conjunctiva of MGD patients is lower than the average of normal patients.[5] With the optimum melting temperature of MGD meibum reported at 41.5°C and reports of some at-home heating therapies delivering between 37-40°C on the inner tarsal conjunctiva, an argument can be made that at-home therapies might not be enough to liquify and mobilize inspissated meibum.[6,7]

One in-office procedure for melting and mobilizing abnormal meibum in those glands that we have had success with is the Systane iLux. We recommend this procedure to patients when meibomian gland secretion quality and quantity is low on examination and a sufficient number of glands are visible on imaging. The light emitting diode (LED) technology works by emitting light that gets absorbed by pigments (melanin and hemoglobin) in the eyelid. The pigments convert the light energy to heat, which is then transferred to the surrounding tissues, including the meibomian glands. The Systane iLux emits light at two wavelengths (568 nm and 850 nm), as each wavelength targets specific pigments and depths of penetration. The device heats the eyelid to 40-42°C and maintains it above 40°C during the heating period, which can be 40 seconds or more. After the heating phase, the built-in expression function immediately follows, allowing efficient mobilization and evacuation of the abnormal meibum, without losing temperature. The immediate transition from melting to expression enhances the efficiency and efficacy of the treatment.

Our patients have success with the treatment, and the results in our practice have been consistent with recently published data showing that Systane iLux can be effective in improving meibomian gland secretion scores and symptoms by as early as one week after treatment (Figure 1).[8] Patients reported that frequency and severity of burning, dryness, eye fatigue, and soreness symptoms were reduced by one week after treatment[8] Meibomian gland secretion scores (MGSS) were increased almost 3-fold on a scale of 0-45, with zero representing no secretions.[8] When efficacy

Figure 1. Improvement in meibomian gland secretion score seen by one week after Systane iLux treatment.



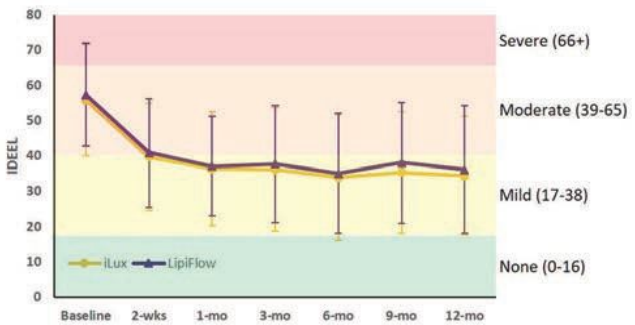


was evaluated over time against Lipiflow (Johnson & Johnson Vision), Systane iLux was non-inferior to Lipiflow at all timepoints, including 12 months.[9] For the Systane iLux treatment group, the average severity of symptoms was in the moderate range at baseline and was in the mild range at 12-months (Figure 2).[10]

Furthermore, the mean meibomian gland secretion score changed by >12 units by 2 weeks and >16 units by 12 months.[9] These results show that an in-office treatment like Systane iLux can provide therapeutic and sustained level of heat to effectively melt MGD meibum and improve symptoms quickly.

Systane iLux[2], which is the latest version of Systane iLux, has a high-resolution display, image and video capture capabilities, including infrared imaging of the meibomian glands. Having a portable handheld device to image, educate, treat, and monitor MGD patients means that clinicians and staff can now offer effective MGD treatments in space-saving, staff-efficient and resource-friendly way.

Figure 2. Changes in IDEEL Symptom Bother score over 12 months for Systane iLux and Lipiflow.



MGD can be debilitating for many people, including contact lens wearers, preoperative and postoperative patients, as well as digital device users. We recommend identifying and managing MGD early and aggressively. An in-office heating and expression treatment, like Systane iLux, can help kickstart an MGD patient's journey to recovery.

IMPORTANT PRODUCT INFORMATION

Indication: The Systane® iLux2® is indicated for the application of localized heat and pressure therapy in adult patients with meibomian gland dysfunction (MGD), which is associated with evaporative dry eye, and to capture / store digital images and video of the meibomian glands.

Potential Adverse Reactions:

Potential adverse effects may occur because of the procedure. These effects include but are not limited to, the onset or increase in: eyelid/eye pain requiring discontinuation of the treatment procedure, eyelid irritation or inflammation, temporary reddening of the skin, ocular surface irritation or inflammation (e.g., corneal abrasion, conjunctival edema or conjunctival injection (hyperemia)), and ocular symptoms (e.g., burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

Attention: Please refer to the User Manual for a complete list of contraindications, instructions for use, warnings and precautions for the Systane® iLux2®.

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UPDATE YOUR GLAUCOMA PRESCRIBING PROTOCOLS

Treatment options continue to evolve, with new meds and methods to consider.

BY SHALEEN RAGHA, OD, CATHERINE HOGAN, OD, AND ANDREW RIXON, OD
MEMPHIS

In recent years, management of glaucoma has changed considerably, adding an enhanced prostaglandin analog, an entirely new class of drugs and a new sustained-release delivery system. The discussion with patients now includes laser therapy as a first-line treatment option that diminishes concern for patient adherence and ocular surface disease. Every patient will have a unique approach; however, the diagnosis or risk of glaucoma should be definitive before starting or changing glaucoma treatment.

The Big Players

Recently published studies indicate long-term risk of glaucoma in ocular hypertensive patients. Approved by the FDA in 2017 for primary open-angle glaucoma (POAG) and ocular hypertension (OHT), Vyzulta (latanoprostene bunod 0.024%, Bausch + Lomb) is a topical ophthalmic solution made up of latanoprost, which promotes uveoscleral outflow, and butanediol mononitrate, which increases conventional outflow.[1]

Most glaucoma drops only alter uveoscleral outflow, but in a healthy eye the majority of outflow occurs via the trabecular meshwork (TM). Butanediol mononitrate donates nitric oxide, a molecule deficient in glaucomatous eyes, which relaxes the trabecular meshwork, thus increasing aqueous outflow.[2]

The VOYAGER study showed Vyzulta to be more effective than latanoprost 0.005% by ~1.23mm Hg when observing diurnal intraocular pressures (IOPs).[3] Two noninferiority studies, LUNAR and APOLLO, established Vyzulta QD to be more effective than timolol 0.5% BID (32.0% compared to 27.6%).[2]

Vyzulta also has better 24-hour efficacy compared with timolol, which is crucial for elevated nocturnal IOP, indicated by the CONSTELLATION study.[4] Large IOP fluctuations and high nocturnal IOP spikes are evident especially in progressive low-pressure glaucomas, and Vyzulta provides significant IOP lowering in normal-tension glaucoma.[5] Side effects, similar to other prostaglandins, include mild hyperemia (16.7%), irritation (11.9%), eyelash changes (16.7%) and iris and periorbital tissue pigmentation (4.0% and 3.2%, respectively).[4,6]

Historically, prostaglandins have been prescribed first due to their highly effective yet safe profile. Up until now, combination drugs involving prostaglandin did not exist. With Vyzulta's higher efficacy and once-daily dosing, patient adherence can improve, reducing risk of glaucomatous progression. Given these merits, Vyzulta serves as an excellent first-line therapy, but can also be used as second-line if desiring to avoid surgery.[2]

As stated above, the conventional outflow pathway is responsible for the majority of aqueous outflow. Similar to nitric oxide-donating drugs, rho-kinase (ROCK) inhibitors enhance outflow through the TM. This is accomplished by decreasing actin and myosin-driven cellular contraction and reducing extracellular matrix protein production.[7] Additionally, ROCK inhibitors demonstrate neuroprotective

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Dr. Ragha is an assistant professor at Southern College of Optometry (SCO) and practices in the areas of primary care and ocular disease. She is a Fellow of the American Academy of Optometry. **Dr. Hogan** is a clinical instructor at SCO and practices in the areas of ocular disease and minor optometric procedures. She is a Fellow of the AAO. **Dr. Rixon** is an attending optometrist at the Memphis VA. He has achieved Glaucoma Diplomate status through the AAO and is a member of the Optometric Glaucoma Society. They have no financial disclosures.

potential in animal studies and improved anterior and posterior segment vessel density in humans, measured by OCT angiography.[8-11]

The first ROCK inhibitor to be approved in the United States was Rhopressa (netarsudil 0.02%, Aerie) in 2017. Beyond its ROCK inhibition, it has inhibitory action against norepinephrine transporter (NET), making it a ROCK/NET inhibitor. NET inhibition causes vessel constriction and reduction of blood flow to the ciliary processes, therefore reducing aqueous production and lowering IOP. Similarly, NET inhibition reduces episcleral venous pressure through vasoconstriction, accounting for greater than a third of netarsudil's IOP lowering effect.[12,13]

Multiple Phase III studies (ROCKET 1, 2 and 4) have shown that netarsudil QD is at least equivalent to timolol 0.5% BID in patients with POAG and OHT. A 2015 study comparing various concentrations of netarsudil to latanoprost determined that netarsudil was ~1mm Hg less effective than latanoprost for patients with IOP of 22mm to 36mm Hg, but netarsudil was equally effective for patients with IOP below 26mm Hg. Accordingly, netarsudil may be more effective in patients with lower baseline IOPs and might be a preferred choice in the management of patients with lower pressure glaucomas.[14]

Across all studies, netarsudil has been shown to decrease IOP by between 20% and 40%, which is similar to currently recommended first-line therapies.[15] Netarsudil's range of use is broad, as it has recently proven to be effective in patients already on maximal medical therapy (average of three or more medications in this study) whose remaining options previously would have been surgical.[16]

Netarsudil is well-tolerated, with the most common adverse event being conjunctival hyperemia (54.4%). These vascular changes found in studies and in practice are not surprising given the established vasodilatory effects of ROCK inhibitors, distinct from NET inhibition vasoconstriction. Mild, reversible corneal verticillata (20.9%) and conjunctival hemorrhage (17.2%) were also noted.[17] In summary, research validates the versatility of once-daily administration of netarsudil as a safe, convenient and effective medication across a wide spectrum of management needs.

Photo: Abagail Kirk, OD

Vyzulta, Rhopressa and Rocklatan are novel drops to consider for glaucoma patients.

In 2019, Rocklatan (Aerie) was introduced as a fixed-dose combination of netarsudil 0.02% and latanoprost 0.005%, dosed once nightly. Combining the two medications provides an option that has four mechanisms of action: increased uveoscleral and trabecular outflow, decreased aqueous production and episcleral venous pressure. MERCURY 1 and MERCURY 2 were Phase III studies that confirmed the superiority of Rocklatan to its individual components, netarsudil and latanoprost. The studies found that 82% of patients ultimately had an IOP ≤18mm Hg, 30.9% achieved at least a 40% reduction over baseline and 60% achieved a 30% reduction in IOP.

The side effect profile is similar to those of the component medications and includes conjunctival hyperemia (63%), instillation site pain (23%), conjunctival hemorrhage (13%) and verticillata (17.6%).[9] With its broad mechanism of action, Rocklatan is a substantial enhancement to a well-established medication. It provides tremendous potential to supersede current prostaglandins and should receive strong consideration on all eligible patients when initiating therapy.

Setbacks

Although these agents are proven to work in clinical trials, there are many barriers to success with any new therapy. For one, drug novelty comes with a few setbacks, including lack of prescribing familiarity and high costs. As drugs enter the market, insurance coverage and reimbursement challenges may impact patient access to it. Manufacturer coupons and patient assistance programs can provide cost-lowering solutions depending on patient eligibility.[18,19] Next, chronic use of topical ophthalmic drugs can lead to ocular surface disease due to toxicity and inflammation. This complex issue leads to discontinuation of drops, as patients do not typically suffer from discomfort or pain from glaucoma but do feel dry eye symptoms.

The most widely used preservative, benzalkonium chloride, can have harmful effects especially over time.[20,21] Alternative preservatives, available in brand-name drugs, seem to be less damaging to the ocular surface. Preservative-free options may show the least toxicity; however, the active ingredient can sometimes lead to ocular surface disease. Over-the-counter lubricants or prescription drops for ocular surface disease can be

OHTS UPDATE: TWO DECADES OF DATA

Early publications from the Ocular Hypertension Treatment Study (OHTS) showed that treatment of OHT (mean baseline IOP of ≥24.9mm Hg) was associated with a reduced risk of developing glaucoma (five-year risk of 4.4% when treated vs. 9.5% when observed). It showed that observed patients developed POAG an average of 2.7 years earlier than those who were treated. It also identified important factors to help accurately predict the risk of developing POAG, stratified into low, medium and high groups. Phase II discovered that for most patients delaying treatment in the observation group (treated after 7.5 years) only had a small amount of glaucomatous damage compared to the initial treatment group.[52]

Recently published in 2021, Phase III looked at 20-year follow-up data from OHTS, specifically incidence and severity of POAG in one or both eyes. After adjustment to exposure to treatment, the 20-year cumulative incidence of POAG in one or both eyes was 45.6% overall, 49.3% in the original observation (treated after 7.5 years) group and 41.9% in the original treatment group. The incidence of disease was greater in Black participants vs. other races (55.2% vs. 42.7%). Incidence breakdown by risk group was as follows: 31.7% in low risk, 47.6% in medium risk and 59.8% in the highest risk group. The 20-year incidence of visual field loss was 25.2%, with higher mean deviations for patients with bilateral optic disc deterioration and visual field loss compared with patients with unilateral optic disc deterioration and visual field loss.

Although there was a low incidence of visual impairment, 11% of patients ended up with visual acuity worse than 20/40 and 1.2% of patients worse than 20/200. More intensive treatment was needed in 18.1% of OHTS participants, requiring at least one surgical procedure across the life of their management.[53] Accordingly, the initial diagnosis of OHT does not always indicate a benign process will unfold.

Another major finding of Phase III was that the likelihood of developing glaucoma within the 20-year study was roughly equivalent to the likelihood of death (total of 483 POAG cases and 515 deaths). This statistic, although morbid, further informs our prognostic conversations with patients.[53]

Ultimately, although Phase III of OHTS has added to our knowledge, it remains that clinicians need to evaluate all patient risks, including age, health status and personal preferences. A discussion with the patient is warranted. Inform them of their individual risks and develop a plan to meet their needs. Observation or postponing treatment, as long as there is vigilant monitoring of both structure and function, is reasonable, as is treatment when the potential burden of disease outweighs the burden of treatment.[54]

effective, but use of multiple drops in additional to glaucoma therapy can decrease patient adherence and be more costly.[21]

Medication adherence is one of the biggest barriers to success, with nonadherence rates being as high as 80%.[22] In addition to bothersome side effects, other factors influencing nonadherence include forgetfulness, cognitive impairment, health illiteracy, affordability and incorrect administration.[22,23]

Knowledge of this reality, availability of newer drug delivery systems, and broader acceptance of first-line laser treatment offers a solution to lack of patient adherence, while contributing less damage to the ocular surface, leading to a more controlled, comfortable patient.[21,24]

Implants

One recently approved glaucoma therapy embraces intervention by direct intraocular delivery of a drug whose action is sustained for a substantial length of time, while subsequently decreasing the burden of adherence placed on the patient.

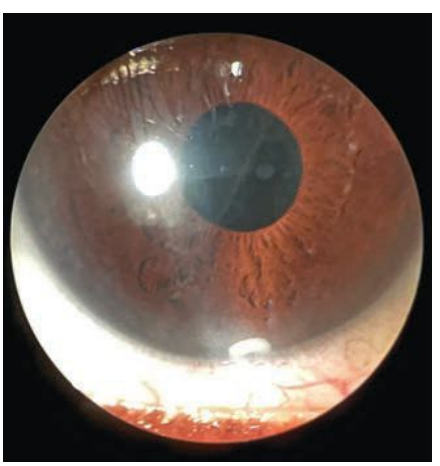
In March 2020, Durysta (bimatoprost intracameral implant, Allergan) became the first sustained-release intracameral implant to become FDA-approved for IOP lowering in patients with POAG and OHT.[25] Durysta contains 10µg of bimatoprost within a rod-shaped, biodegradable, solid polymer drug delivery system that is 200µm in diameter and 1.1mm in length.

The delivery platform is the same as that used to deliver Ozurdex (dexamethasone, Allergan). The implant is supplied preloaded on a single-use, 28-gauge applicator designed to facilitate injection directly into the anterior chamber, typically settling in the inferior iridocorneal angle.

Once injected, the implant is designed to directly target the iris/ciliary body interface, acting to increase aqueous outflow through both the conventional and uveoscleral outflow pathways and provide slow and continuous release of bimatoprost over four to six months.[25-27]

Two Phase III 20-month studies (ARTEMIS 1 and ARTEMIS 2) showed that the mean IOP over 12 weeks after bimatoprost implantation is consistently lower than timolol maleate 0.5% BID when compared directly. In both ARTEMIS 1 and 2, implants were administered on day one, week 16 and week 32 of the study. IOP was then assessed at week 52 after the last implantation. Interestingly, the proportion of subjects requiring no additional treatment for a year after the third implant were 82.1% in ARTEMIS 1 and 77.5% in ARTEMIS 2. By comparison, in Phases I and II only 36% of subjects did not require additional treatment for a year after a single implant.

It has been proposed that the extended duration of action after sequential implants may be explained by remodeling of the aqueous humor outflow pathway mediated by matrix



Anterior segment slit lamp photo of Durysta implant still visible at six-month follow-up.

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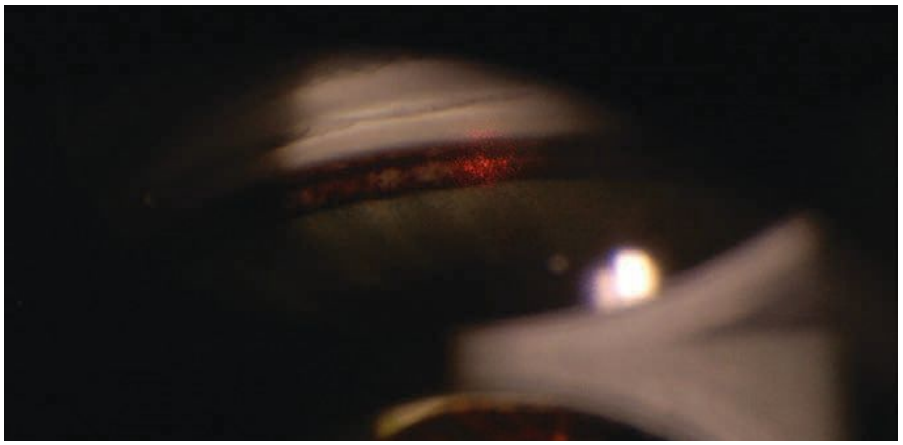

In SLT, the laser straddles the TM.

metalloproteinase (MMP) ,which can lead to lower episcleral venous pressure.[25,27,28] At present, Durysta is approved for one solitary administration. Although its long-term utility will depend on achieving an indication for repeated administration, the value of Durysta as an additional management tool is apparent.

Overall, sustained-release bimatoprost is safe, with a low incidence of serious adverse events in all three study phases. The most common of these were conjunctival hyperemia, eye irritation, foreign body sensation, conjunctival hemorrhage and eye pain, all of which were typically reported as secondary to the implantation procedure rather than the medication itself and abated within two weeks of the procedures.

The most common serious ocular adverse event was corneal endothelial cell loss. A ≥20% decrease in central endothelial cell density (CECD) was reported in 0% (ARTEMIS 1 and 2) of patients after the first administration of the 10ug implant, in 2.3% and 0.6% of patients after the second administration, in 4.1% and 3.5% after the third administration and in 10.2% and 8.1% of respective study eyes at month 20. Implants were removed in 3.6% and 2.9% of respective patients, most commonly for corneal edema or central endothelial cell loss.

Notably, patients in the ARTEMIS studies were required to have a CECD ≥1,800 cells/mm^2 in order to exclude patients with significant corneal endothelial dysfunction.[25,27,28] Ultimately, Durysta should not be used in patients with corneal endothelial dystrophy or those who have previously undergone corneal transplantation.

Although intracameral implantation is an excellent option, a 2016 study of glaucoma patients revealed that 55% preferred daily drop use over more aggressive treatments.[29] A patient survey by the Glaucoma Service at Massachusetts Eye and Ear determining acceptance of six different drug delivery approaches showed an acceptance rate of 30% for an injectable anterior chamber implant. Contrarily, patients with more severe disease were more likely to consider alternatives to eye drops.[30]

Meanwhile, physicians may have a more positive outlook on sustained drug delivery, as a 2014 survey of ophthalmologists showed that 88.9% would consider using a newer drug delivery mechanism (*i.e.*, a drug-eluting contact lens).[31] However, these studies and surveys on patient and practitioner attitudes were done prior to FDA approval of any sustained delivery devices; thus, having tangible options in current practice may shift attitudes beyond what was previously theoretical.

Laser Focus

Another procedure that looks beyond pharmacotherapy and eliminates risk of medication nonadherence is selective laser trabeculoplasty (SLT), which uses a 532nm Q-switched, frequency-doubled Nd:YAG laser to deliver three nanoseconds of short-pulse therapy to the pigmented TM to increase aqueous outflow.[32] Histopathological studies have shown SLT's selective photothermolysis causes less collateral damage than its predecessor, argon laser trabeculoplasty, where heat generated within the pigmented cells dissipates and damages the surrounding TM tissue.[32,33] SLT also increases aqueous outflow via biological changes such as modulation of gene expression, cytokine secretion, matrix metalloproteinase induction and TM remodeling.[32,34-36]

SLT received FDA approval in 2001 and has become increasingly more common as adjunct and first-line therapy for reduction of IOP in POAG and OHT patients.[37-40] Clinical technique relies on the physician's gonioscopy abilities, identification of the pigmented TM and knowledge of appropriate laser spot size and energy level.

Many studies have evaluated degrees of treatment and energy settings with respect to IOP lowering, resulting in current practice standards of 50 to 100 shots applied over 180° to 360° with energy levels around 0.6mJ to 1.4mJ.[37-40] Successful application of laser is confirmed with visual feedback of minor tissue reaction or small microbubbles after each laser shot.[40]

SLT does reduce IOP but its effect subsides over time. Average IOP reduction following SLT is around 21% to 29% at six months, 16% to 30% at 12 months, 7% to 28% at two years, 24% to 25% at three years, 23% to 29% at four years, 22% to 32% at five years and 22% at six years. Treatment success is widely accepted to be an IOP reduction of greater than 20% from baseline.

Reported success rates vary from 66% to 75% at six months and diminish to 11% to 31% at five years.[40,41] The repeatability of SLT mitigates this diminished return; it is safe and

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EXAM TOOLS

Every examination should incorporate these assessments, which can provide more objective and quantitative information.

Funduscopy

- Examine superior-temporal and inferior-temporal rim tissue and RNFL.
- Distinguish cupping greater than pallor and visible laminar reconfiguration.
- Expect a large cup-to-disc ratio for large optic discs.

Gonioscopy

- Studies indicate gonioscopy is the least-performed clinical examination tool in glaucoma care.[55]
  - —*Our take:* gonioscopy differentiates glaucoma types (*i.e.*, PG, PXG, NVG, ACG, traumatic) along with the anterior segment evaluation.

IOP

- Despite being the only modifiable risk factor, note that other pressures—such as episcleral venous pressure, ocular perfusion pressure and cerebrospinal fluid pressure—influence optic nerve health.
- Recognize true diurnal/nocturnal IOP varies.
- Consider multiple untreated readings.
- Acquire corneal thickness and hysteresis.

OCT

- Review raw scan quality and retinal layer segmentation.
- Differentiate among ischemic, compressive and anomalous causes.
- View neuroretinal rim thickness, circumpapillary RNFL thickness and macular ganglion cell thickness, looking for glaucomatous patterns of loss.

Visual field

- The World Glaucoma Association recommends at least two reliable visual fields within six months and two more visual fields within 18 months to establish an accurate baseline.[56]
  - —*Our take:* personalize test strategy (24-2C, 24-2, 10-2) based on topographical analysis of tissue.
  - —*Our take:* assist in staging of severity of glaucoma.
  - —*Our take:* focus on expanding and/or deepening of defect density and confirm defects are repeatable.
- Discern slow progression from large, drastic changes caused by other conditions.

effective to provide additional SLT treatment to previously treated TM, with retreatment providing similar IOP reduction as primary SLT.[42,43]

SLT is not indicated if TM cannot be visualized. Therefore, it is paramount that the referring or procedure-performing physician have sufficient gonioscopy skills to recognize SLT candidacy. SLT is not always successful in isolation, which emphasizes the need to individualize treatment for each patient, including custom IOP target ranges and thorough assessment for disease progression with funduscopy and ancillary testing.[44,45]

The general increase in the incorporation of SLT has driven the need to compare the procedure to topical therapies. Review of current literature shows that SLT is as effective as topical medication for IOP control, including prostaglandin analog monotherapy or different topical medications used in combination.[29,38,40,46] Of note are the results of the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial, which investigated the efficacy of SLT as a primary treatment compared with topical medications in treatment-naïve patients over 36 months.

Primary SLT patients were at their individualized IOP targets over more clinical visits during the 36-month period compared with patients treated with eye drops (93% vs. 91%). Furthermore, the primary SLT group also demonstrated less disease progression and fewer surgical interventions. Drop-free and disease-controlled primary SLT patients, after one or two SLT therapies, equaled 85% at 12 months, 79% at 24 months and 74% at 36 months.

Other study factors of the LiGHT Trial were health-related quality of life and cost-effectiveness. Primary SLT was found to be more cost-effective than topical therapy over 36 months, but the health-related quality of life was not significantly different between the two groups.[45] Thus, SLT is considered a safe and effective alternative to topical therapy for POAG and OHT patients, while avoiding adverse effects associated with eye drops, which may improve treatment adherence and overall patient quality of life.[40,44,45]

Other benefits of SLT include delivery of treatment using a short, outpatient method with quick recovery and a good safety profile.[40] There are limited adverse events related to SLT; the LiGHT Trial deemed all to be transient and self-limiting, with the most common adverse event being ocular discomfort immediately post-procedure (23% of patients).[45] This data supports the belief that SLT is a flexible treatment option for a variety of patient care scenarios, especially when topical therapy is not best practice. Implementing SLT into the optometric practice will strengthen overall glaucoma care by increasing the opportunity for patients to receive prompt treatment while reducing ocular surface disease and patient nonadherence.[21,24,47]

Clinical Takeaways

Prior to initiating or changing any treatment, the diagnosis of glaucoma should be confirmed, as treatment is

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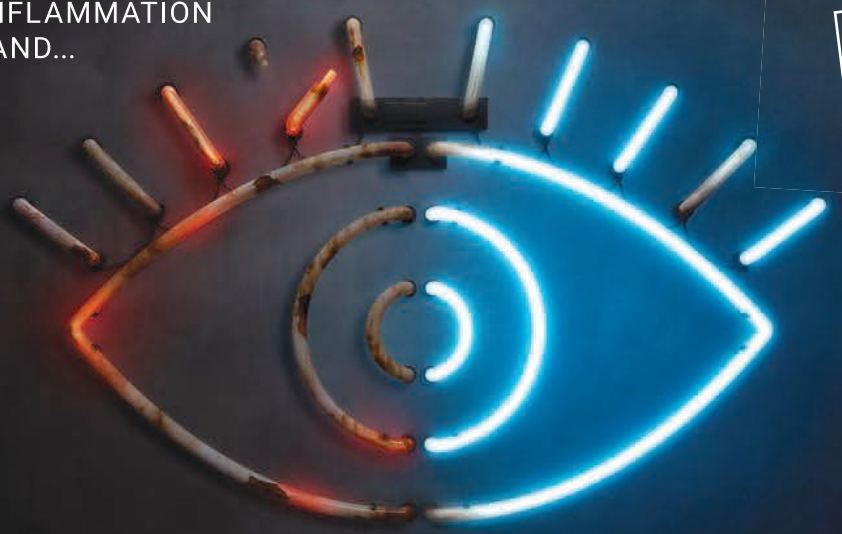

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‡For patients 65 years of age or over who have a supplemental prescription plan — Medicare Part D or Medicare Advantage — or have no coverage (paying cash).

Indications and Usage

For steroid responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe and chronic anterior uveitis, corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies for which a corticosteroid is indicated and where the risk of superficial bacterial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

Important Safety Information

CONTRAINDICATIONS:
Most viral disease of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures. Hypersensitivity to any components of the medication.

WARNINGS & PRECAUTIONS:

- **IOP increase –** Prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.
- **Aminoglycoside sensitivity –** Sensitivity to topically applied aminoglycosides may occur.
- **Cataracts –** Posterior subcapsular cataract formation may occur.
- **Delayed healing –** May delay healing and increase the incidence of bleb formation. Perforations of the cornea or sclera have occurred. Slit lamp biomicroscopy, and fluorescein staining should be conducted.
- **Bacterial infections –** May suppress host response and increase secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- **Viral infections –** Use with history of herpes simplex requires great caution. The course and severity of many viral infections of the eye (including herpes simplex) may be exacerbated.
- **Fungal infections –** Fungal infections of the cornea may occur and should be considered in any persistent corneal ulceration.
- **Use with systemic aminoglycosides –** Total serum concentration of tobramycin should be monitored.

ADVERSE REACTIONS:
The most frequent adverse reactions (<4%) to topical ocular tobramycin are hypersensitivity and localized ocular toxicity, including eye pain, eyelid pruritus, eyelid edema, and conjunctival hyperemia.

The reactions due to the steroid component are increased intraocular pressure with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

The development of secondary infection has occurred. Fungal infections of the cornea may occur. Secondary bacterial ocular infection following suppression of host responses also occurs.

Non-ocular adverse events (0.5% to 1%) included headache and increased blood pressure.

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

[a]Randomized, investigator-masked, active-controlled, parallel-group trial conducted at 7 private practice clinical sites in the United States with 122 adult patients who had moderate to severe blepharitis/blepharoconjunctivitis.[1]

[b]Multicenter, double-blind, parallel-group, single-dose study of 987 patients receiving a single dose of TOBRADEX ST or TobraDex ophthalmic suspension.[2]

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Santen

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Brief Summary

This Brief Summary does not include all the information needed to use TOBRADEX ST safely and effectively. Please see Full Prescribing Information for TOBRADEX ST at MyTobraDexST.com.

INDICATIONS AND USAGE

TOBRADEX ST is a topical antibiotic and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Instill one drop into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, dosage may be increased to one drop every 2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

CONTRAINDICATIONS

Nonbacterial Etiology: TOBRADEX ST is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Hypersensitivity: Hypersensitivity to any component of the medication.

WARNINGS AND PRECAUTIONS

IOP increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.

Aminoglycoside sensitivity: Sensitivity to topically applied aminoglycosides may occur.

Cataracts: May result in posterior subcapsular cataract formation.

Delayed healing: May delay healing and increase the incidence of bleb formation after cataract surgery. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids.

Bacterial infections: May suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

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

Fungal infections: Fungal infections of the cornea are particularly prone to develop with long-term use. Fungal invasion must be considered in any persistent corneal ulceration.

Use with systemic aminoglycosides: Use with systemic aminoglycoside antibiotics requires monitoring for total serum concentration of tobramycin.

ADVERSE REACTIONS

The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including eye pain, eyelids pruritis, eyelid edema, and conjunctival hyperemia. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Non-ocular adverse events occurring at an incidence of 0.5% to 1% included headache and increased blood pressure.

The reactions due to the steroid component are: increased intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

Secondary Infection.

The development of secondary infection has occurred. Fungal infections of the cornea are particularly prone to develop with long-term use. Fungal invasion must be considered in any persistent corneal ulceration. Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

Pregnancy and Nursing Mothers

There are no adequate and well controlled studies in pregnant women. TOBRADEX® ST ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when TOBRADEX® ST is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

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

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typically lifelong and affects quality of life. Unfortunately, misdiagnosis of glaucoma is quite common.[48] Patients should not be treated based on IOP alone, especially if the risk of conversion from OHT to POAG is low, based on age or corneal thickness (see *"An OHTS Update"*).[49] Confirmation of glaucoma requires sound clinical fundoscopy and interpretation of technology (see *"Exam Tools"*).[50,51]

Glaucoma management is continually evolving, with new drug trials and longevity studies showing effectiveness of treatment. Practitioners should avoid remaining stagnant in their treatment protocols and patient discussions. ■

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ANTI-VEGF IN 2022: INNOVATION AND AMBITION

Let's review our current options, what has been recently approved and what lies in the future.

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It was long theorized that regions of ischemic retina released some type of unknown factor that promoted growth of new vasculature (*i.e.*, neovascularization). The molecule now known as vascular endothelial growth factor (VEGF) was discovered and found to be present in much higher concentrations in eyes with neovascularization than in those without. Animal models also revealed that artificially creating a hypoxic retina led to increased VEGF and that injecting VEGF into the eye induced iris neovascularization and neovascular glaucoma.[1]

The development of anti-VEGF injections has provided a medical option to patients with certain posterior segment issues that simply didn't exist before. New compounds continue to be developed and tested to better resolve retinal issues.

A New Treatment Emerges

In the early 2000s, innovation leapt forward and anti-VEGF compounds began to be used therapeutically. The first was intravenous bevacizumab (Avastin, Genentech), which was FDA-approved for the treatment of colon cancer in February 2004. Soon after, an anti-VEGF molecule was approved for the eye: pegaptanib (Macugen, originally Eyetech/Pfizer, now Bausch + Lomb), approved in December 2004 for treatment of neovascular age-related macular degeneration (wet AMD).

Pegaptanib's success was short-lived, as the much more affordable off-label use of bevacizumab (reconstituted for intravitreal injection by a compounding pharmacy) and the 2006 FDA approval of Genentech's on-label wet AMD drug ranibizumab (Lucentis) both eclipsed Macugen in clinical efficacy.[1]

In 2011, aflibercept (Eylea, Regeneron) would be approved for wet AMD based on the results of the VIEW trials that showed aflibercept dosed every two months was not inferior to ranibizumab dosed monthly.[2] Ranibizumab and aflibercept would later be approved for the treatment of diabetic macular edema (DME) and macular edema from retinal vein occlusions (RVO). In addition, ranibizumab is approved for treatment of myopic choroidal neovascularization (CNV). Off-label use of bevacizumab remains widespread due to its significantly lower cost.

During this anti-VEGF revolution, wet AMD went from a nearly untreatable sentence of blindness to a much more manageable condition with early intervention. In addition, patients with diabetic retinopathy (DR) and RVO had new hope of vision-improving therapies that didn't rely on destructive laser treatments (*Figure 1*). Some might have thought that the rest would be history, but it was just getting started.

Ranibizumab and Aflibercept

Regarding DR treatment, anti-VEGF was primarily used for many years to treat DME per ranibizumab and aflibercept's FDA approval. Panretinal photocoagulation (PRP) was still the mainstay treatment for proliferative DR (PDR), and patients with non-proliferative DR (NPDR) without macular edema were predominantly monitored without treatment.

Observation of patients who were receiving injections anecdotally showed regression of retinal and

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iris neovascularization and general improvement of the retinopathy as a whole, which gave rise to the following questions:

(1) Can we treat patients with proliferative disease with anti-VEGF alone, and how does this stack up to treatment with PRP?

(2) If we treat patients without proliferative disease and without DME prophylactically with anti-VEGF, can we reverse retinopathy and prevent sight-threatening complications?

DRCR Protocol S compared the safety and efficacy of ranibizumab with PRP for the treatment of PDR. Ranibizumab was found to be noninferior to PRP, and secondary outcomes showed superior visual acuity gains and less visual field loss when using ranibizumab over PRP. In addition, patients in the ranibizumab arm were less likely to develop center-involving DME.[3]

The downside of ranibizumab over PRP is increased treatment burden, with ranibizumab patients requiring much more frequent treatment than those receiving PRP. Patient compliance therefore remains a chief concern. If patients do not comply with frequent office visits and injections, there is risk of disease progression and blindness. The decision to treat a PDR patient with anti-VEGF, PRP or a combination of both remains very patient-specific for most physicians.[3]

The PANORAMA trial evaluated the use of aflibercept vs. sham injection in patients with moderately severe to severe nonproliferative diabetic retinopathy without macular edema. The primary endpoint was a two-step regression on the DR severity scale (DRSS), and secondary endpoints were proportion of patients developing vision-threating complications such as development of retinal or iris neovascularization and center-involving DME.

The study had three treatment arms: aflibercept dosed q16 weeks after three initial monthly doses and one eight-week interval dose, aflibercept dosed q8 weeks after five initial monthly loading doses with PRN dosing after week 56 and sham injections (control group).

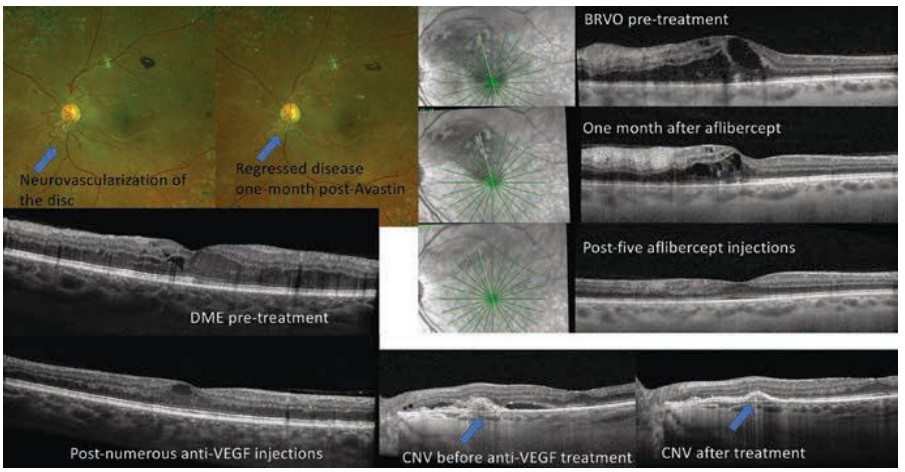

Fig 1. Anti-VEGF injections are beneficial for a wide array of posterior segment complications.

One-year results showed that 80% of patients in the q8 week arm, 65% of patients in the q16 week arm and 15% of patients receiving sham met the primary endpoint of at least a two-step reduction on the DRSS. In addition, patients in both the q8 and q16 week arms had significant reduction in their risk of developing vision-threatening complications and center-involving diabetic macular edema. Two-year results showed continued benefit of fixed-interval injections in this patient population.[4]

The results of Protocol S and the PANORAMA study resulted in new approvals for ranibizumab and aflibercept. Ranibizumab was approved in 2017 for all forms of DR, and then aflibercept followed with the same approval in 2019. These results and approvals show the potential for disease regression and suggest a benefit for earlier intervention for severe NPDR patients without macular edema, shifting the paradigm towards earlier referral and treatment. The use of anti-VEGF for this patient group, who traditionally has been monitored, is still very patient- and physician-dependent (*Figure 2*).

Novel Drugs and Targets

For about a decade, these three drugs—bevacizumab, ranibizumab and aflibercept—remained our only anti-angiogenic weapons in the treatment arsenal. The pursuit continues for novel drugs with increased durability, efficacy and even lower cost to ultimately improve patient visual outcomes and decrease treatment burdens.

At present, there is another influx of innovation and potential occuring, with two new anti-VEGF agents (brolucizumab and faricimab) and a new delivery method for ranibizumab (Susvimo) all approved since 2019, and numerous others in the pipeline. Some of these try to revamp what is already available while others seek to inhibit new targets with entirely new mechanisms of action.

Beovu. The 2019 approval of Beovu (brolucizumab, Novartis) gave patients access to four options for anti-VEGF therapy. The strong clinical trial outcomes through all phases of study led many providers to predict Beovu would grab a significant market share in the space. Why did that not happen? With expanded usage, providers began noticing incidents of intraocular inflammation. Most were mild and self-resolving, but some exhibited signs of severity, including branch artery occlusions and vitritis.[5] These patients suffered vision loss as a result. This led to an extensive investigation, multiple presentations at national meetings and many new publications all directly dealing with the issue of intraocular inflammation and Beovu.[6,7]

The overall incidence of intraocular inflammation was found to be around 4%.[7] This would be considered an acceptable risk for most agents, but

when compared with what amounts to no intraocular inflammation risk with Avastin, Eylea and Lucentis, Beovu's adoption faltered and most providers stopped using it. This has left it as the option of last resort for most retina specialists, which is reflected in its diminished market share and its limited commercial prospects going forward.

The authors of this article continue to advocate for its use as it seems to be the strongest available agent and is the best option for patients with an under-response to Eylea. When choosing to use Beovu in a patient, a more extensive informed consent process is advisable with full disclosure of the increased risk of intraocular inflammation compared with other agents. We have notably not seen a case of intraocular inflammation in our practice for over two years despite continued significant use in our practice.

Conbercept (Chengdu Kanghong Biotechnology). This agent has been approved by the Chinese FDA since 2013 for treatment of wet AMD, making it one of the most widely used anti-VEGF therapies for this condition worldwide. Conbercept is a recombinant fusion protein composed of the second IgG domain of VEGFR1 and the third and fourth domains of VEGFR2 to the constant region (Fc) of human IgG1.

There are more than 30 clinical trials regarding conbercept for Chinese and the United States FDA approval. These trials concern the international market for wet AMD, non-AMD choroidal neovascular membranes, DR and RVO macular edema, and retinopathy of prematurity. Trials also evaluate the drug in combination with systemic chemotherapy for treatment of retinoblastoma.[8] There are also studies on treatment of neovascular glaucoma and macular edema secondary to uveitis.

The Aurora, Phoenix and Panda clinical trials have evaluated various dosing (0.5mg vs. 2mg) and treatment regimens such as three loading doses followed by monthly, every eight to 12 weeks or PRN. All these regimens have indicated this recombinant anti-VEGF is an effective treatment for wet AMD.[9-12]

Conbercept's potential benefit is its higher binding affinity than other anti-VEGF drugs (30x higher than Lucentis and Avastin). Clinical trial results will help to reveal how this translates to real-world treatment. Thus far it is comparable to other currently commercially available anti-VEGF in clinical trials; therefore, this would also likely be another available agent in the United States and other countries for treatment of wet AMD and other conditions in which this class of drugs have been successfully used over nearly two decades.[13] We cross our fingers for its approval in the US.

Faricimab (Vabysmo, Genentech). This is a bispecific antibody that targets both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2). The latter is a growth factor involved in the angiogenesis pathway. It is upregulated by hypoxia and is present in increased levels in eyes with DR and wet AMD.[14] Faricimab has been evaluated thus far across four Phase III trials (TENYA and LUCERNE for wet AMD and YOSEMITE and RHINE for DME) showing noninferior visual gains vs. aflibercept. Of great interest, about half of patients receiving faricimab could successfully extend treatment to four months. Use of faricimab for the treatment of macular edema from RVO is currently being evaluated in the Phase III trials COMINO and BALATON.[15] In January 2022, the FDA granted approval for Vabysmo for wet AMD and DME treatment.[16]

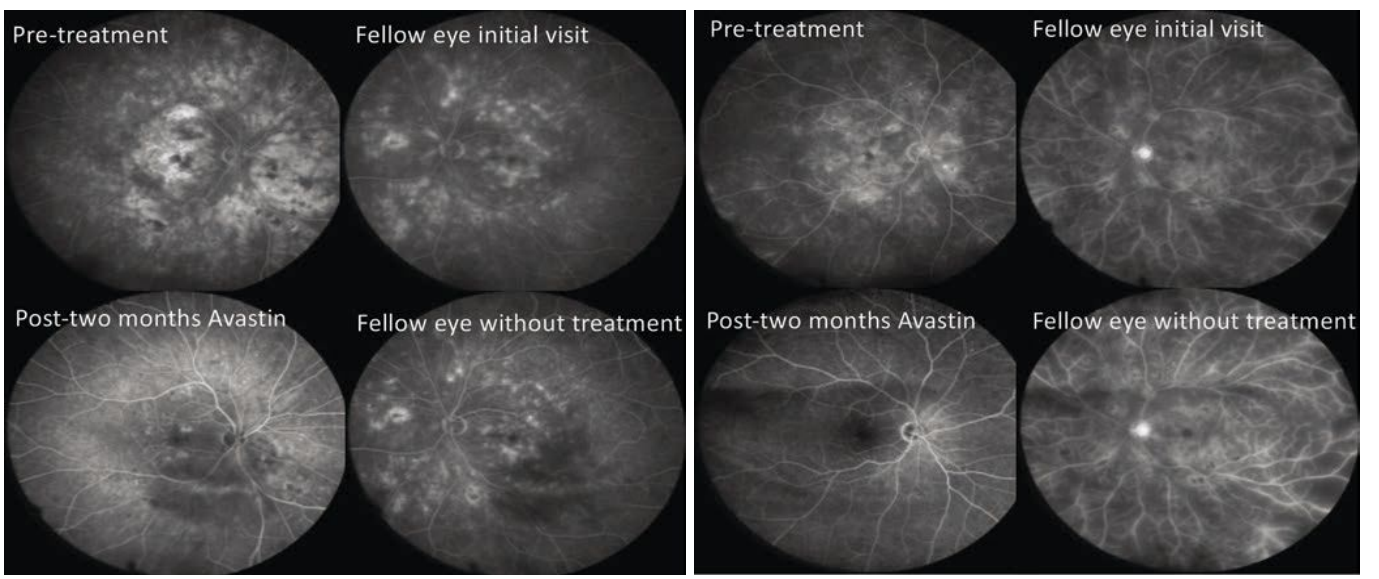

Fig. 2. Periodic treatment with anti-VEGF has been shown to reverse severity of retinopathy, a benefit beyond simply treating DME and proliferative disease. This figure shows fluorescein angiographies of two separate patients with severe NPDR. The OD of each patient was treated with two monthly injections, while the OS was monitored. Notice the profound improvements in the treated eyes vs. lack of improvement in the untreated fellow eyes.

No Prescription No Problem

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Drs. Cunningham and McDonald are paid consultants for Alcon.

Help Ocular Allergy Itch Patients Get Prescription Strength Relief Without the Rx

Millions of patients suffer from ocular allergies and need relief from their symptoms,[1] which is why all eye-care professionals need to be on alert. Both of our practices are surgically oriented and yet we still see many patients suffering from ocular allergy symptoms that need to be addressed prior to performing any procedures. That is why we are excited that the prescription-strength olopatadine products from Alcon are available over-the-counter (OTC), making it easier for our practices to make sure patients can get the relief they need when they need it. For our practices, we no longer need to devote staff time and resources to deal with health insurance companies or pharmacies, while remaining confident our OTC recommendations provide the same active ingredients and

formulations that we have prescribed for years. For our patients, it's "no prescription, no problem". They can get fast-acting relief from ocular allergy itch whenever they need it (Pataday® OTC products are available online and wherever eye drops are sold) and at an accessible price, typically less than the cost of the average prescription co-pay.

Allergies are common problems that can impact patients year round,[2,3] with patients reporting the symptom itchy eyes almost as often as congestion.[4,5] Ocular allergy can be disruptive to patients' lives; in a survey of patients experiencing ocular allergy symptoms, more than two-thirds rated symptoms as "bothersome" to "extremely bothersome."[6] In our practices, we educate patients on the benefits of treating ocular allergy itch at the source and recommend Pataday® OTC ocular allergy itch relief drops.

Targeted Dual Mechanism of Action Relieves Itch at the Source

All Pataday® OTC products contain olopatadine,[7-9] formerly the #1 prescribed ocular allergy itch relief ingredient. With its targeted dual mechanism of action, olopatadine both selectively blocks the binding of histamine to H1 receptors and prevents the release of histamine from the mast cell, along with release of other pro-inflammatory mediators, providing fast and effective relief of ocular allergy itch.[10,11]

Recommending the Right Pataday® for Each Patient

Pataday® OTC treatments offer different options so we can tailor recommendations to best meet each patient's needs. Our Pataday® recommendation is based on a few easy questions, such as "When do your eyes feel itchy?," "Are your eyes itchy all day or only during certain activities?," and "Does having itchy eyes impact your sleep?" For those who are bothered by ocular allergy itch all day even when indoors, we recommend Pataday® Once Daily Relief Extra Strength. It is the first and only 24-hour ocular allergy itch relief drop available OTC and provides relief within minutes.[12] For our patients who do not require a full 24 hours of relief or who may only have situational allergies—like when mowing the lawn or visiting a friend with pets—Pataday® Once Daily Relief provides up to 16 hours of relief from ocular itch and Pataday® Twice Daily Relief provides up to 8 hours of ocular itch and redness relief.[8,9,13]

With millions of ocular allergy sufferers, every practice will have patients who experience ocular allergy itch. It is important that we make our patients aware of how to manage their symptoms and recommend the prescription strength Pataday® OTC product that is right for them.

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Byooviz (ranibizumab-nuna, Samsung Bioepis). This medication is a biosimilar of ranibizumab; that is, a biologic medical product highly similar to an already FDA-approved agent that has been shown to be equally safe and effective. A biologic is a medication that is manufactured in, synthesized from or extracted from a biological source. This differs from a traditional drug that is created through chemical synthesis and not through use of biological sources. Biosimilars can be compared with a generic form of a traditional, chemically synthesized drug. Byooviz was approved by the FDA in September 2021 for the treatment of wet AMD, macular edema from RVO and myopic CNV. It has not been approved for treatment of DME or DR.[17]

Byooviz's approval came after a Phase III trial of 705 patients, 634 of whom continued treatment into week 48, showed similar efficacy and safety between Byooviz and ranibizumab. Concerns regarding Byooviz center primarily around safety. Although biosimilars are comparable to generics regarding biologics, the manufacturing process of biologic medical products may be more important in the safety and efficacy of the drug than for non-biologics. In addition, there is concern that unsuspected adverse effects may be uncovered when going from use in hundreds of patients in a clinical trial to thousands in real-world treatment.[17]

The main advantage of the Byooviz will likely be cost, allowing patients to potentially get the benefits of ranibizumab without the high price tag, increasing patient access and lowering healthcare cost. The exact cost of the medication is still unknown, and it is not planned to be released in the US until June 2022.

While the concept of biosimilars is somewhat unfamiliar to many physicians, one survey's results suggested most physicians would consider using an anti-VEGF biosimilar once available for their patients. With numerous other companies moving forward with additional ranibizumab and even aflibercept biosimilars, time will ultimately tell how readily the medications will be accepted and incorporated into practice.[18,19]

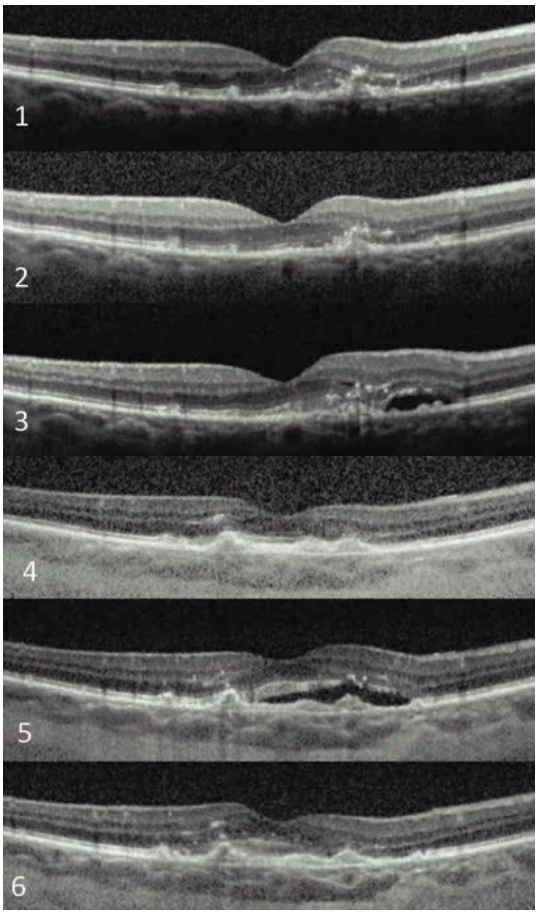


Fig. 3. An exudative AMD patient who has required over 20 anti-VEGF injections in nine years to maintain 20/40 visual acuity. These are a few snapshots in time during the course of her treatment.

Ocular-specific bevacizumab. Outlook Therapeutics is a biopharmaceutical company in late clinical trial stages anticipated to launch ONS-5010, the first commercially available bevacizumab, under the tradename of Lytenava, for treatment of wet AMD, DME and branch RVO (BRVO).[20,21]

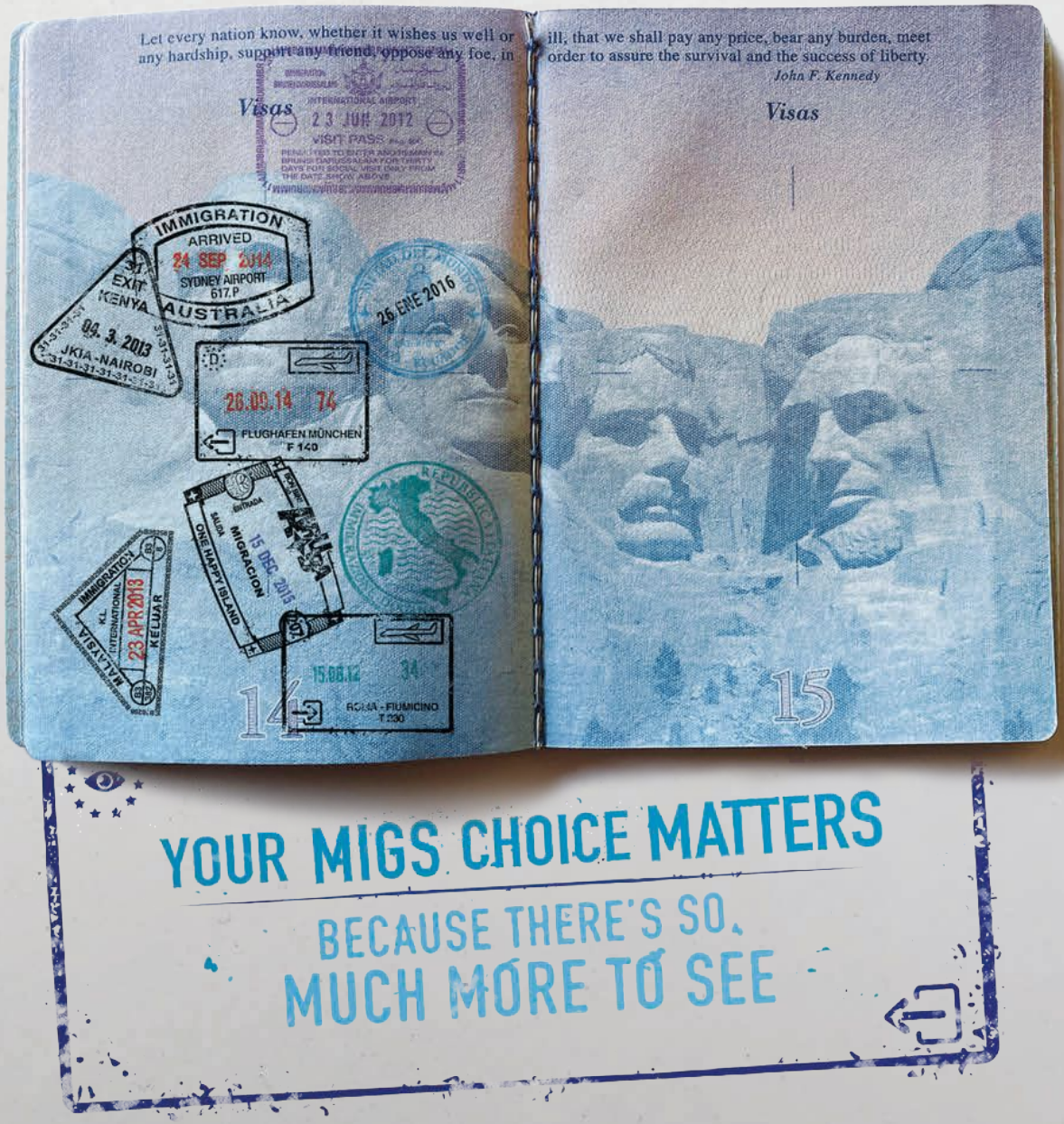
The NORSE noninferiority clinical trials have been comparing ONS-5010 with ranibizumab indications of the above-mentioned conditions. Outlook is hoping to launch this product as a potential first-line anti-VEGF therapy based on historical use of anti-VEGF, particularly off-label bevacizumab, for ophthalmic conditions over nearly two decades. The introduction of an FDA-approved commercially available bevacizumab for ophthalmic use has the potential to reduce consumer confusion about off-label drug use, reduce chance of adverse events particularly endophthalmitis, offer better quality control and shift the burden of product liability. However, much of this will be seen in the future based on price point, insurance coverage and the expanded novel and biosimilar agents.

Novel Delivery Systems

Despite all the success with anti-VEGF therapy, the downside of the high burden of treatment—six or more intravitreal injections per year—remains an obstacle (*Figure 3*). Patients are still tied to frequent office visits and need for recurrent treatments that, while tolerable, many find uncomfortable to some extent and inconvenient to attend to (often, a family member must accompany the patient, increasing inconvenience and disruption).

Longer-acting and more efficacious drugs as described above may be part of the solution for this problem, but additionally advances in medication delivery are likely to be a game changer. These novel delivery systems try to address the question of how we can get these sight-saving medications into the eye without subjecting our patients to frequent, sometimes life-long, injection regimens.

Susvimo (Roche). This was an important FDA approval in the retina space for 2021—a refillable, implantable delivery system for sustained release of ranibizumab. It is currently approved for wet AMD and has ongoing clinical trials for DME and DR.[22] It delivered on its promise of sustained treatment effect with a much lower burden of care across all trial phases for wet AMD. It showed equal visual gains as ranibizumab injected monthly, and over 98% of patients with Susvimo could go six months before requiring a refill (*Figure 4*).[23]



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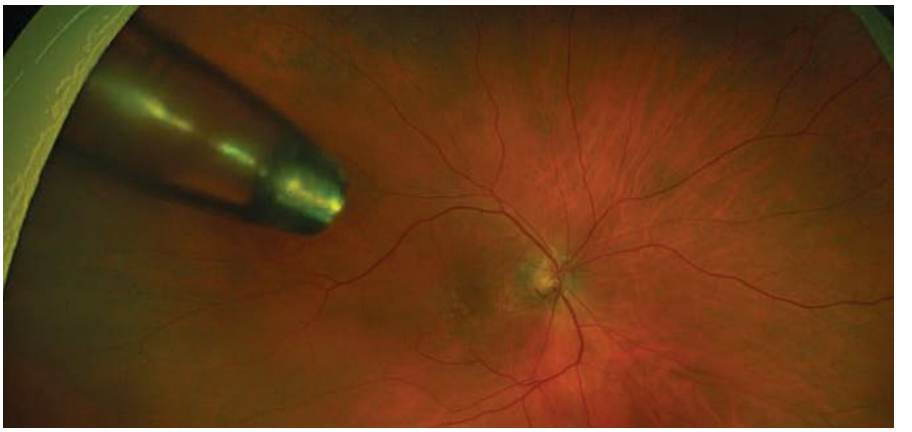

Fig. 4. Ultra-widefield image of wet AMD patient treated with the Susvimo implant.

The procedure itself evolved as it progressed through the approval process. Early problems with vitreous hemorrhage were reduced with more meticulous surgical techniques centered around hemostasis and wound creation. The grain of rice–sized implant is not sutured in place but instead fits snugly inside the eye with only a minimally elevated flange resting on the external sclera. This allows for easy refills in the clinic at six-month intervals through the small central septum visible underneath the semitransparent conjunctiva and Tenon's capsule.[22]

Rollout is limited to start with only the principal investigators at certain sites performing the first commercial implantations. John Kitchens, MD, was the first to implant one commercially, and our site in Memphis was the first to implant Susvimo in Tennessee a week later.

Clinical trial results indicate a good safety profile with an approximate 2% endophthalmitis risk, most of which was linked to conjunctival retraction. Implant dislocations were rare as well.[23] The risk of these two problems is dramatically reduced by employing good surgical practices including perfect wound creation and meticulous closure of conjunctiva and tenons. This is an implant designed to last the entirety of the patient's lifetime with near infinite refill ability. It is a good option for active patients struggling with the burden of frequent office visits and injections.

Gene Therapy Delivery

There are a multitude of active gene therapy trials currently underway in the retina space. We will focus on one company that is showing great promise. RegenxBio has multiple gene therapy trials underway for wet macular degeneration. The biologic agent under study is a modified adenoviral vector containing a genetic package that, through the process of transfection, enables retinal pigment epithelial cells to produce a modified ranibizumab-like molecule that then dramatically reduces the number of intravitreal injections a patient requires.[24,25]

Public results so far are outstanding, with a clinically significant reduction in intravitreal injections given for those dosed via vitrectomy and subretinal delivery and a clinically significant reduction in intravitreal injections with those dosed via an in-office suprachoroidal procedure.[24,25]

The vitrectomy-based procedure requires great skill and a fine touch but is able to be performed with off-the-shelf vitrectomy supplies. The suprachoroidal in-office procedure requires the use of a novel suprachoroidal delivery syringe with a specially designed needle tip to safely enter the suprachoroidal space. Both procedures are exceptionally well-tolerated, with only a few patients exhibiting non-severe inflammation following treatment.[24,25] These treatments have the potential to alleviate VEGF-driven diseases while at the same time dramatically

decreasing the frequency of intravitreal injections.

In addition to RegenxBio, the company Adverum Biotechnologies is using a viral vector intravitreally for expression of aflibercept with positive Phase I results, now moving into Phase II. Numerous gene therapy trials with various other anti-angiogenic targets are also underway.[26]

Long-term Effects

Anti-VEGF therapy in many patients diagnosed with wet AMD, DME and macular edema due to RVO can turn into long-term treatment, as these are chronic conditions needing chronic care. Studies and experience have shown us that gaps and lapses in therapy can have detrimental consequences and result in poor outcomes.[27] However, long-term invasive therapy of any medical condition can have its own set of consequences and setbacks. These include reduced patient's adherence to recommended treatment regimen due to a variety of reasons and barriers, including cost, increased chance of adverse events and reduced effectiveness of therapy (tachyphylaxis).

In regards to long-term and multiple intravitreal injections, adverse events and tachyphylaxis are also possible but are not great concerns. With regards to adverse events, endophthalmitis is the greatest concern, the incidence of which is approximately one in 3,000 injections (0.033%).[28] Ocular inflammation and occlusive vasculitis has been reported with these injections and particularly became a concern with repeated injections of brolucizumab.[7,29,30] This resulted in an FDA label update in June 2020 warning prescribers.

Tachyphylaxis has also been noted with intravitreal injections. This is an uncommon finding in treatment of wet AMD in a minority of patients.[31] Cases of recalcitrant DME as well as macular edema associated with RVO are also encountered clinically, in which case alteration of medication to other anti-VEGF agents or to intravitreal steroidal agents was considered to alter the course of the disease.[32-35]

Clinical Takeaways

Intravitreal delivery of anti-VEGF medications has dramatically improved visual outcomes of patients suffering from numerous retinal pathologies. The use of some widely accepted drugs has been going on for over 15 years now, but new possibilities and innovations continue to expand options for patients and physicians, allowing for better patient access, improving efficacy and easing the burden of treatment. ■

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PEER REVIEWED

TAMING INFLAMMATION IN DRY EYE DISEASE

It triggers—and perpetuates—this all-too-common condition. Here's a look at the therapies available to fight it.

BY PAMELA THERIOT
SHREVEPORT, LA

The prevalence of dry eye disease (DED) is rising around the world and with that comes a plethora of new treatments. Given its multifactorial causes, chronic nature and potential for progression, ongoing persistence with treatment is required. In treating DED, optometrists must understand the pharmacology of the disease and the importance of reducing inflammation. It's is the chief culprit in dry eye, and in order to fight it, we have to understand how anti-inflammatories work.

The Tear Film and Ocular Surface Society's (TFOS) Dry Eye Workshop II (DEWS II) definition recognizes the impact of inflammation to the ocular surface, saying, "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1]

Several therapeutic agents are available to break the vicious circle of dry eye and help prevent chronic disease progression, and there is also a wide variety of non-pharmacological interventions with the potential to reduce inflammation.

We will review the pathogenesis of inflammation in DED, what perpetuates it and how to mitigate it, along with the therapies currently available. With so many tools in our toolbox, there's never been an easier way to knock out inflammation.

Inflammation's Role in DED

The central mechanism of DED is a vicious cycle where inflammation plays a key role. The inflammation may be stimulated either by desiccating or hyperosmolar stress—both of which lead to ocular surface damage.[2]

A growing body of research on the role of inflammation in the pathogenesis of DED has led to the recognition of dysregulation of immune responses on the ocular surface.[3] Regardless of the etiology of DED, both chronic inflammation (T-cell mediated immune response) and tear hyperosmolarity are the most common factors in its chronicity.[2]

Hyperosmolarity can be caused by many factors, including destruction or degeneration of the lacrimal gland, conjunctiva and meibomian glands, damage to corneal nerves (in the case of ophthalmic surgery, corneal infections, long-term contact lens abuse or long-term topical medication use), reduced tear production due to systemic medications (such as beta blockers, oral antihistamines, birth control pills and hormone replacement therapy) and meibomian gland disease.[2]

Hyperosmolarity induces inflammation in human limbal epithelial cells by increasing expression and production of pro-inflammatory cytokines and chemokines such as IL-1b, TNF-α and IL-8.[4] Interleukin (IL)-1 is one of the most widely studied cytokines accompanying dry eye. An increase in the pro-inflammatory forms of IL-1 (IL-1α and mature IL-1β) and a decrease in the biologically inactive precursor IL-1β have been found in the tear film of dry eye patients.[5]

Infiltration of T-cells into the lacrimal functional unit (which includes

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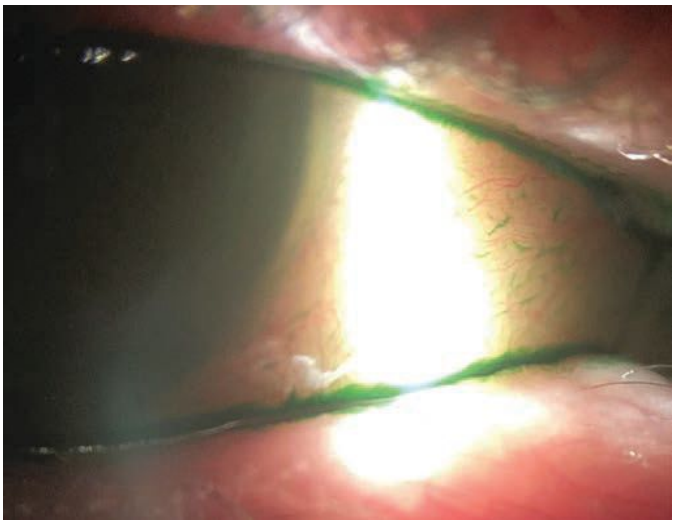
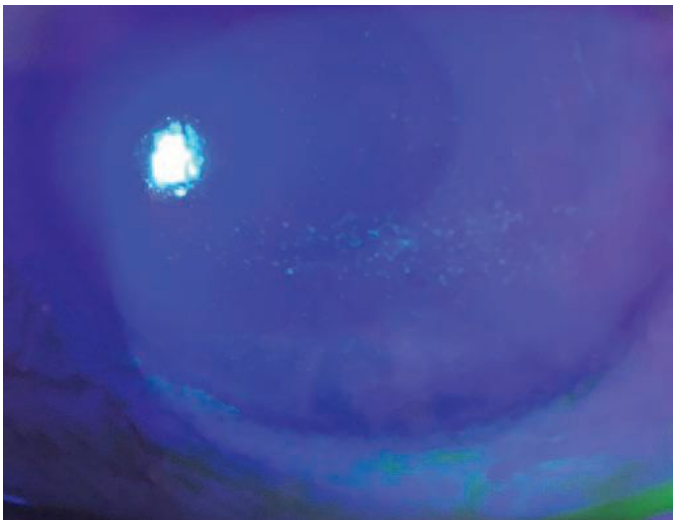


Lissamine green vital dye, shown here in a dry eye patient with inflammation, helps visualize devitalized cells on the conjunctiva.



This patient demonstrates moderate staining of corneal epithelium with sodium fluorescein.

the lacrimal gland, goblet cells in the conjunctiva and meibomian glands) is known to result in chronic inflammation.[6] Inflammatory mediators released from recruited T-cells and tear hyperosmolarity accentuate cellular damage and loss of epithelial and goblet cells, leading to a vicious cycle of tear film instability and chronic inflammation.[7] Throughout the inflammatory response, immune cells release proinflammatory cytokines and chemokines, which recruit more immune cells and eventually results in a vicious cycle of inflammation that does not resolve.[2]

An appreciation of the basic immunological factors associated with DED is essential for appropriate management of patients with the disease.[8] DED immunopathophysiology is characterized by four stages: initiation, amplification, recruitment and reinitiation.[9] Dessicating stress leading to hyperosmolarity is a great example of the initiation of the vicious circle of DED.[2]

Dry eye patients (whether with a concomitant autoimmune disease or not) have conjunctival inflammation manifested by T-cell infiltrates and upregulation of CD3, CD4 and CD8. They also demonstrate lymphocyte activation markers CD11a and HLA-DR.[10] Inflammation in dry eye disease is mediated by lymphocytes.[11] MAP kinases were found to stimulate the production of inflammatory cytokines, including IL-1, TNF-α and MMP-9, and thereby causing ocular surface damage.[12]

Vital dyes are also valuable in the detection of ocular surface damage often seen alongside inflammation. The use of sodium fluorescein or lissamine green vital dyes is particularly helpful in identifying and visualizing the devitalized cells on the conjunctiva.[13]

How to Mitigate Inflammation

It is widely recognized that inflammation has a significant role in dry eye disease. It promotes the breakdown of the ocular surface and leads to symptoms of irritation and, commonly, visual disturbance. Anti-inflammatory treatments are a mainstay of the management of dry eye disease, as they inhibit the expression of inflammatory mediators on the ocular surface and act to restore a healthy tear film and decrease the signs and symptoms.[14]

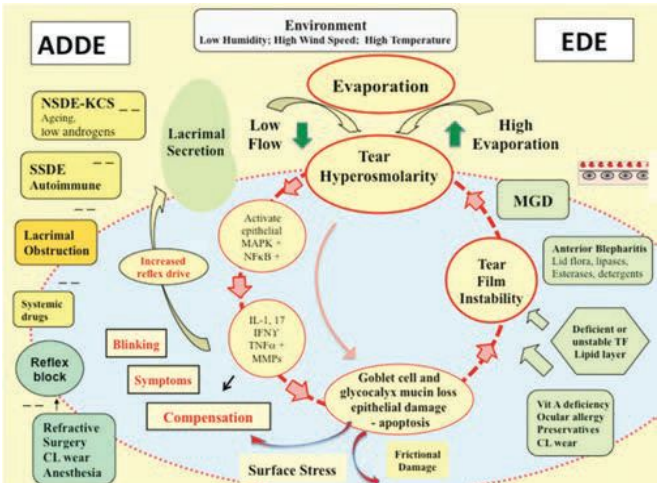
Current anti-inflammatory therapies include corticosteroids (lotepredenol, prednisolone, fluoromethalone and dexamethasone), immunomodulators (cyclosporine and liftegrast) and oral tetracyclines (doxycyline). Let's briefly review how these modalities interrupt the inflammatory process.

Corticosteriods. These agents work by suppressing cellular infiltration, capillary dilation, fibroblast proliferation and collagen deposition, and they also stabilize intracellular and extracellular membranes.[14] Corticosteroids also interfere with the synthesis of pro-inflammatory molecules.[15] Several clinical studies have demonstrated the effectiveness of topical steroids for treatment of dry eye.[16]

While topical corticosteroids demonstrate effective interruption of the inflammatory and immune response cycle of DED, long-term use can present complications such as ocular hypertension, cataract formation and opportunistic infections.

Eysuvis. Although corticosteroids are an effective treatment for DED, long-term use is associated with cataract development, increased intraocular pressure (IOP) and opportunistic infections.[17] Eysuvis (loteprednol etabonate 0.25%,) an ocular corticosteroid, breaks down rapidly after administration to the ocular surface tissues and reduces the risks associated with other topical steroids, as well as potentially decreases harmful side effects such as elevated IOP and cataract formation.[18]

Loteprednol was formulated based on the "inactive metabolite approach," where it is metabolized by hydrolysis. In both *in vitro* and *in vivo* metabolism of loteprednol, an inactive, hydrophilic metabolite was easily



The "vicious cycle" of inflammation that drives chronic dry eye.

eliminated from the body.[19] Loteprednol etabonate was retro-metabolically engineered 30 years ago to reduce the common risks of topical ocular steroids, including IOP elevation and cataract formation.[20] The Lotemax family of loteprednol-based products has been long used off-label in dry eye patients.

The tear film's ability to efficiently remove foreign particles during blinking can pose challenges for topical drug delivery. Traditional eye medications in the form of drop solutions and suspensions are cleared from the ocular surface by blinking before the drug is able to penetrate conjunctival and corneal epithelium.[18] On the ocular surface, the function of the mucus barrier is to protect cellular surfaces and maintain water balance.[21]

Eysuvis is an ophthalmic nanosuspension that delivers loteprednol to the anterior eye using mucus-penetrating particles (MPPs). This method has been shown to efficiently penetrate the mucus barrier and reach the ocular surface tissues quickly.[18] The MPP formulation of loteprednol etabonate ophthalmic suspension has favorable properties for treatment of ocular surface disease.[18] In pre-clinical studies, 0.5% loteprednol vs. 0.4% loteprednol in MPP formulation was shown to have a 3.6-fold higher concentration in the corneal epithelium after just five minutes.[22]

Dry Eye Flares. The TFOS DEWS II report describes an initial presentation of DED that may involve intermittent symptoms or "emerging episodic dry eye."[23] However, there's evidence in a variety of settings for the existence of periodic flares of DED in the context of ongoing disease.[18]

Patients who present with mild signs and symptoms often do not require chronic immunomodulatory therapy, such as cyclosporine A or lifitegrast, as some patients may also experience periodic flares on a seasonal or episodic basis and would benefit from short-term therapy when their symptoms flare-up.[16] DED flares may occur episodically in response to specific triggers, such as low humidity, air conditioning and windy conditions.[24]

In patients with episodic disease, appropriate therapy at the time of a flare-up could potentially break the vicious circle of inflammation early in its process and help prevent further damage to the ocular surface. Flares of otherwise mild DED may benefit from short-term steroid therapy.[18]

When an episode of ocular surface discomfort and a flare of DED is diagnosed, a short course of Eysuvis may relieve the patient's symptoms and potentially calm the vicious cycle of inflammation.[18] The Stride 1 Phase III clinical trial with 914 patients demonstrated a clinically significant change in ocular discomfort score after only eight days.[25]

Cyclosporine A. Topical formulations of cyclosporine A (CsA) provide a broad-based approach to DED treatment by decreasing inflammation and improving the integrity of the ocular surface with few systemic effects.[9] Due to CsA 0.05% immunomodulating effects, it can be the therapy of choice for patients with DED and an underlying autoimmune disease vs. using a corticosteroid.[13] The immunomodulator is the better treatment due to the chronic nature of autoimmune disease because it can control the inflammation over long periods of time.[13]

CsA has principal pharmacologic action of suppressing the activation and function of T-lymphocytes, acting as an immunosuppressant and inhibitor of cell death.[14] The reduction in inflammation, via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland, is thus thought to allow enhanced tear production.[26] Topical cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis.[9,27]

TABLE 1. DISTINGUISHING PROPERTIES OF CORTICOSTEROIDS AND INNUMOSUPPRESSANTS

	Corticosteroids	Immunomodulators
Decrease Signs	Suppress inflammation	Decrease inflammation
Decrease Symptoms	Decrease redness, irritation and discomfort	Increase tear production
Ocular Side Effects	Increase IOP, cataract formation, opportunistic infections	Stinging and redness at instillation site
Efficacy	Work quickly	Can take two weeks to six months to notice symptomatic improvement
Mechanism of Action	Reduce inflammation by inhibiting phopholipase A2, which blocks the cyclooxygenase and lipoxygenase pathways	Inhibit T-cell activation

Most Patients With Dry Eye Suffer Acute Episodes of Worsening Symptoms—*DRY EYE FLARES*[1-3]

MAKE EYSUVIS THE FIRST Rx THERAPY FOR YOUR PATIENTS WITH DRY EYE

1

Patients with ***MILD-TO-MODERATE DRY EYE WHO USE ARTIFICIAL TEARS*** but still suffer acute episodes of worsening symptoms (Dry Eye Flares)

2

Patients initiating or currently using ***DAILY CHRONIC Rx THERAPY*** (ie, lifitegrast, cyclosporine) for induction and/or breakthrough Flares

EYSUVIS is *THE FIRST AND ONLY FDA-APPROVED SHORT-TERM* (up to two weeks) Rx treatment for the *SIGNS AND SYMPTOMS* of Dry Eye Disease

INDICATION

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Contraindication:

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

Warnings and Precautions:

Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.

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

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

Adverse Reactions:

The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

Please see Brief Summary of Prescribing Information for EYSUVIS on the next page.

References: 1. Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of dry eye flares: a patient questionnaire survey. Presented at: AAO 2019; October 12-15, 2019; San Francisco, CA. **2.** Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of symptomatic dry eye flares: results from patient questionnaire surveys. Poster presented at: AAOPT 2019; October 23-27, 2019; Orlando, FL. **3.** 2020 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc.

EYSUVIS®
(loteprednol etabonate ophthalmic suspension) 0.25%
THE FAST FLARE FIGHTER

kala PHARMACEUTICALS

US-EYS-2200025 January 2022
www.EYSUVIS.com

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

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

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

The most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD.

The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data—*Animal Data:* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation—There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for EYSUVIS and any potential adverse effects on the breastfed infant from EYSUVIS.

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.EYSUVIS.com.

Manufactured for:
Kala Pharmaceuticals, Inc.
Watertown, MA 02472

Part # 2026R02

October 2020
Kala®

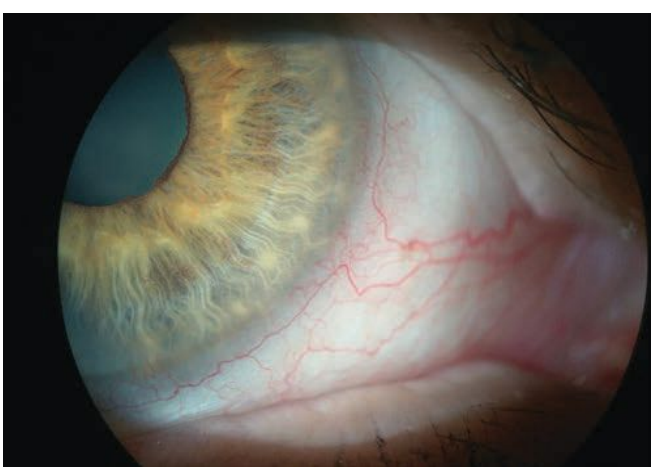
US-EYS-2000115

Cyclosporine A is a calcineurin inhibitor that exerts immunomodulatory effects by blocking T-cell infiltration, activation and the subsequent release of inflammatory cytokines.[28] The action of CsA on T-cells is the primary mechanism for DED symptom improvement; however, its effects may extend beyond T-cell modulation. Twice-daily treatment for two weeks with CsA 0.05% decreased expression of proinflammatory cytokines and chemokines IL-1β, TNF-α, IL-6, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1.[29]

CsA reduces the underlying inflammation associated with DED that interferes with tear production and has fewer ocular complications than steroids

Restasis. Topical CsA was developed to increase tear production in patients with DED who did not respond sufficiently to conservative treatments such as ocular lubricants and lid hygiene. Benefits of using CsA 0.05% has been shown to improve tear production, tear break-up time, and corneal and conjunctival staining scores.[31] Based on BID dosing of CsA 0.05% for three months, 72% of participants were satisfied with their results and 57.2% reported a reduction to mild to no symptoms.[32]

Restasis (cyclosporine A 0.05%) increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with DED.[16] Restasis demonstrated improvements observed in DED increased Schirmer's score and decreased conjunctival staining scores.[31] Additionally, using CsA to decrease ocular inflammation helped reduce mechanical stressors on the eye and improved epithelial integrity.[33] Improvement in the reduction of persistent epithelial defects and reduction in episodes of recurrent corneal erosions occurred after two months of twice-daily dosing of CsA 0.05%, even though these patients had previously been resistant to therapy with corticosteroids.[33]



This patient's injected blood vessels indicate inflammation, which can be seen without any vital dyes.

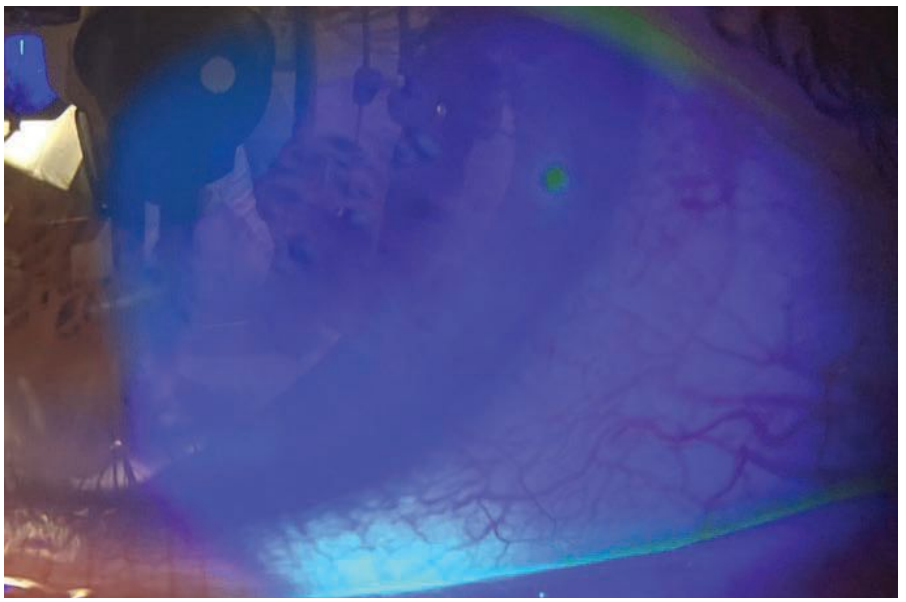
Restasis is safe to use long-term, but can take up to three months before patients notice any improvement.[34] Clinical results show that the time to onset of reduction in ocular surface staining and improvement in visual performance with Restasis is on average six months.[35] Such long lead times to initial efficacy may interfere with patient compliance with treatment in DED, but continued usage is important to attain therapeutic levels of CsA in ocular tissues.[36]

Self-reported adherence with the prescribed twice-daily regimen of topical CsA 0.05% was associated with more rapid onset of reported increase in tear production, as well as greater patient satisfaction and willingness to continue therapy.[37] However, studies have shown that patients with severe dry eye may require more frequent dosing of Restasis than twice daily.[38] Mean corneal fluorescein staining scores and no new-onset symptoms of burning and irritation were reported in participants with graft-vs-host disease and primary or secondary Sjögren's syndrome who increased their dosage of CsA 0.05% from BID to three to four times daily.[38] Thus, newer cyclosporine drugs have come to market to increase the concentration of CsA on the cornea and conjunctiva.[14]

Cequa. A recently introduced cyclosporine product, Cequa (CsA 0.09%) is an aqueous nanomicellar

TABLE 2. COMMONLY AVAILABLE TOPICAL STEROID MEDICATIONS

BRAND NAME	GENERIC NAME	MANUFACTURER	NOTES
Lotemax SM	Loteprednol 0.38%	Bausch + Lomb	Submicron particle size allows penetration to the ocular surface
Lotemax Gel	Loteprednol 0.5%	Bausch + Lomb	
Lotemax Ung	Loteprednol 0.5%	Bausch + Lomb	Preservative-free
Alrex	Loteprednol 0.2%	Bausch + Lomb	
Inveltys	Loteprednol 1.0%	Kala Pharmaceuticals	
Eysuvis	Loteprednol 0.25%	Kala Pharmaceuticals	FDA-approved for dry eye flares
Flarex	Fluoromethalone acetate 0.1%	Santen Pharmaceuticals	
Pred Forte	Prednisolone 1.0%	Allergan	
FML	Fluoromethalone 0.1%	Allergan	
FML Ung	Fluoromethalone 0.1%	Allergan	
FML Forte	Fluoromethalone 0.25%	Allergan	



Seen here is a 2+ conjunctival injection. This redness is a sign of inflammation.

formulation that increases tear production in patients with DED. It aims to increase CsA bioavailability and reduce adverse reactions.[39]

Cequa is different from Restasis due to its nanomicellar delivery system. Hydrophobic interactions of core-forming units drive the micelle formation with a water-insoluble or hydrophobic core and an outer water-soluble or hydrophilic shell. Thus, these nanomicelles are more bioavailable in the precorneal tear film.[36] Aqueous CsA nanomicelle carriers produce rapid improvement in objective signs of DED such as corneal and conjunctival staining as early as four weeks.[30]

The aqueous nanomicellar approach used in Cequa may help enhance and maximize tissue availability of CsA. Therefore, the patient will have improved comfort and compliance and potentially better clinical outcomes in treatment.[30] This nanomicellar formulation allows the medication to penetrate the ocular surface faster and get to work sooner, while reducing the adverse reactions of stinging and burning felt by patients taking Restasis.

Lifitegrast. This agent (brand name Xiidra) targets inflammation by inhibiting T-cell recruitment, T-cell activation and subsequent cytokine release.[40]

Lifitegrast 5% is a small-molecule integrin antagonist that inhibits T-cell mediated inflammation by blocking the binding of two important cell surface proteins (lymphocyte function-associated antigen 1 and intercellular adhesion molecule 1), thus lessening overall inflammatory responses.[40] The role of T-cells is pivotal in the development of cell-mediated immune responses in the eye. Specifically, CD4 positive (+) T helper (TH) 1 and TH17 T cells have been identified as mediators of ocular surface inflammation in DED.[10]

Recruitment and activation of these T-cells at the ocular surface leads to the release of pro-inflammatory cytokines. It is these cytokines that contribute to the damage seen in the ocular surface of DED patients. Therapies targeting T-cells will provide a more efficient means to treat DED.

Since lifitegrast works to inhibit T-cell recruitment and activation, patients taking Xiidra felt relief in as little as two weeks. The majority saw improvement in six weeks and it took others as long as 12 weeks, whereas patients taking Restasis would wait up to three months to feel a similar relief in the reduction of corneal and conjunctival staining.[41,42]

Doxycycline. Tetracycline derivatives uniquely possess both antibacterial and anti-inflammatory properties.[43] Tetracyclines, such as doxycycline hyclate, present immunomodulating properties that inhibit leukocyte movement during inflammation by preventing calcium-dependent microtubular assembly and lymphocytic proliferation.[44] Doxycycline reduces inflammation by decreasing the production of pro-inflammatory cytokines.

In particular, doxycycline has been shown to inhibit c-Jun N-terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase signaling in epithelial cells of the ocular surface exposed to hyperosmolar stress, downregulating the expression of CXCL8 and pro-inflammatory cytokines IL-1β and TNF.[43] Doxycycline hyclate works well in the eye due to its high lipophilicity, which allows it to cross multiple membranes to reach target molecules.[45]

Oral doxycycline can be used long term in low doses to control inflammation on the eye. Studies have shown doses of 40mg daily (or 20mg BID) are effective for anti-inflammatory effects.[44] In a study of eight weeks of oral doxycycline hyclate 20mg dosed BID, there was 80% to 100% clearance of inflammatory lesions and 50% reduction in erythema in patients with rosacea.[44] The antimicrobial mechanism will not be in action at this sub-antimicrobial dose; therefore, it spares healthy bacteria and maintains the body's microbiome.[45]

Doxycycline has been reported to be effective in patients with ocular rosacea by reducing irritation symptoms, improving tear film stability and decreasing the severity of ocular surface disease.[46]

Combining Therapies

It is helpful to combine anti-inflammatory treatments to help patients feel comfortable more quickly.

Loteprednol works quickly and targets T-cells. Cyclosporine prevents T-cell recruitment but may take sever-

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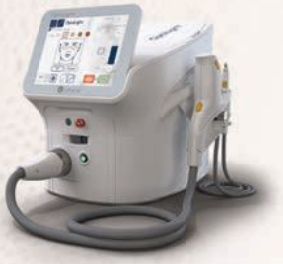

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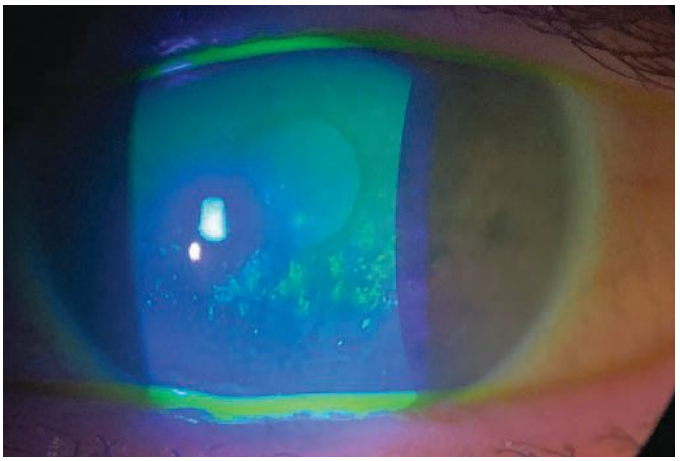
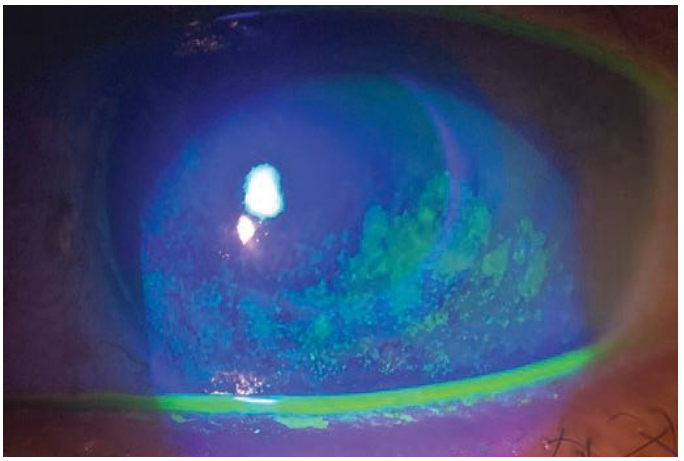


A 2+ band of corneal punctate epithelial erosion in a patient with severe keratoconjunctivitis sicca.



Here is another patient with severe keratoconjunctivitis sicca, this one with active fluorescein staining.

al weeks to begin working.[9] These two mechanisms of action complement one another and, when used together, provide fast relief and long-term safety.[47]

Corticosteroids are often used in conjunction with immunomodulators if there's significant inflammation present on the ocular surface.[13]

Here are three ways topical steroids can be effective in treating DED:

(1) *Alongside an immunomodulator*: Eysuvis or Lotemax may be a helpful adjunctive therapy for patients receiving chronic immunomodulatory treatment for DED, especially those with underlying autoimmune or inflammatory conditions.[18]

(2) *At initiation of immunomodulatory therapy*: When a dry eye patient starts topical immunomodulatory therapy, the loteprednol-based corticosteroid products have the potential to be used as induction therapy to quell ocular surface inflammation and DED symptoms until the new therapeutic agent takes effect.[18]

(3) *Breakthrough symptoms*: Patients using chronic immunomodulatory therapy for DED may still experience periodic episodes of breakthrough symptoms. Topical steroid use could be effective in pulsed doses to treat episodic DED signs and symptoms.[18]

In addition, there is evidence that doxycycline can be used alongside either corticosteroids or immunomodulators without reducing the effectiveness of either treatment.[48] Doxycycline can be used long-term due to its good safety profile and low incidence of bacterial resistance to it at sub-acute dosages.[49] It also pairs nicely with other topical anti-inflammatory properties and does not interfere with the absorption of other medications on the ocular surface.[50]

Takeaways

Reducing or eliminating inflammation will not just help reduce pain and irritation in the eyes, but will give your patients some much needed relief. To get there, it's important to manage DED appropriately and facilitate realistic patient expectations—both of which are necessary to ensure patient satisfaction and compliance with their treatment.

Educating your patients is vital to DED management and should convey the complex and chronic nature of the disease, as well as the potential for progression. Though results will likely not be seen immediately, it's imperative that the duration of medication be fulfilled to ensure inflammation is kicked to the curb. ■

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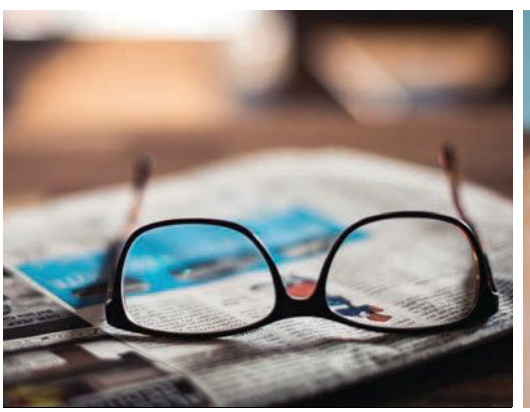
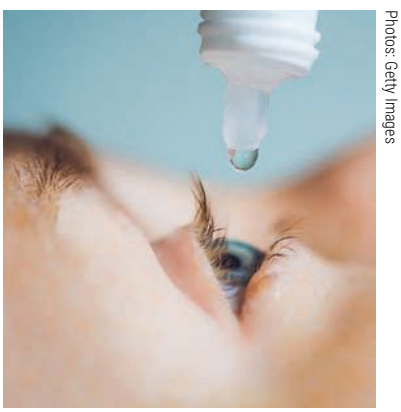
MEDICAL MANIPULATION OF VISION DEBUTS

The first of many pharmaceutical options to alleviate presbyopia gives optometrists a new tool—and new challenges.

BY CATLIN NALLEY
CONTRIBUTING EDITOR





Photos: Getty Images

Eyedrop therapy now challenges the gold standard of corrective lens options for presbyopia. ODs need to understand the pros and cons of each and be candid when discussing them.

With the introduction of the first eye drop for presbyopia, optometrists have another tool in their arsenal to alleviate this vexing condition. As with any new therapeutic approach, it is important to understand the benefits and risks, as well as the implications for clinical practice.

"It is an exciting time in eye care," notes Melissa Barnett, OD, of the University of California, Davis Eye Center in Sacramento and Davis, CA. "With the approval of Vuity (pilocarpine hydrochloride, Allergan), we now have a whole new class of medications at our disposal. And, not only that, we also have a new practice modality and the opportunity to offer our patients more than glasses, contact lenses and surgical options."

Given the prevalence of the condition—there are currently 128 million presbyopes in the United States, and that number will only continue to grow—the implications of a pharmaceutical option are significant, according to Dr. Barnett. "This is just the beginning," she says, while noting there are a number of products in development right now. "Therefore, it is important that doctors of optometry consider the impact that therapeutics like Vuity can have for patients and their practices."

As this new approach is explored in clinical practice, optometrists are tasked with educating patients and helping them determine if this is the right option for their needs and lifestyle. This involves considering the pros and cons of the drug, as well as how it compares to the current standard of care. Corrective lenses may be bothersome, but they set various benchmarks for performance in the minds of the public and the doctors who serve them. A medical alternative that fails to provide comparable results must offer substantial advantages in return for the trade-off to be worthwhile.

Pilocarpine in Practice

Vuity uses the familiar pupil-constricting properties of pilocarpine (at a 1.25% concentration) to temporarily sharpen near vision. In an attempt to

reduce stinging upon instillation, the drug is formulated in such a way that it rapidly adjusts to the natural pH of the tear film.[1]

It received FDA approval in October 2021 for patients with presbyopia based on findings from two Phase III clinical trials that evaluated the efficacy, safety and tolerability of Vuity in presbyopic patients between the ages of 40 and 55. The treatment showed a statistically significant improvement when compared to placebo. The primary endpoint was the ability to achieve three lines of near vision improvement under mesopic conditions without losing more than one line of distance vision at day 30, hour three.[1]

In terms of side effects, the study authors reported that the most common non-serious adverse events were headache and eye redness.[2-4] The research also showed that the effect of the drug was seen as early as 15 minutes, peaked after one hour and then declined over time, lasting for about six hours.

Considerations For the OD

Now that a pharmaceutical option is available for presbyopia, optometrists should be ready to have discussions with their patients that include the benefits and potential adverse events, as well as realistic expectations on performance and cost.

But first, they must identify the ideal candidate for Vuity. "I would have some discussion with any patients experiencing early symptoms of presbyopia—generally after age 40—and those who are in their mid-50s," says Joseph Shovlin, OD, of Northeastern Eye Institute in Scranton, PA, who notes that it's worth remembering contact lens patients may experience near problems earlier than they might with spectacle correction.

To date, Dr. Shovlin has prescribed this treatment to a few patients but cannot yet comment on its durability. "Some of my patients have expressed a dimming of vision effect initially, and most have continued use with less of a dimming effect over time," he explains, while suggesting prescribers stick to the recommended cut-off of 55 years old, since most patients will experience at least some early lens changes at 55 and older.

"Those of us who remember prescribing pilocarpine for glaucoma—when we had just this class along with a beta-blocker—recall the undesirable side effects with patients who had significant cataracts and those who experienced the common side effects of cholinergic muscarinic agonists, namely conjunctival injection and headaches," Dr. Shovlin adds.

Since Vuity's approval, Dr. Barnett has seen significant excitement among her patients, including those who have brought up the treatment themselves. The feedback she has received so far has been positive. "My patients have been very happy with their results and are thrilled to have an option to correct their vision that works. Very few have reported headaches, and if a headache is noticed, it is typically on the first day," she notes.

"We have found that using the drops every morning for a week helps with adaptation," Dr. Barnett adds. "I also ask very detailed questions at the initial examination and in my follow-up to better understand how this treatment fits into my patient's lifestyle."

Justin Bazan, OD, of Park Slope Eye in Brooklyn, has also found early success with the drug. "It has been a welcomed addition to my optometric toolbox," he notes. "For my pre-presbyopes, I give them the heads up and get them thinking about it. It often gets a 'wow' and reminds them that I'm a doc who is passionate about their care and who stays current in the industry."

Other optometrists have expressed frustration and seen variable results. The main issues include the aforementioned dimming of vision, particularly while indoors, and inconsistent duration of effect. Some noted that the drug stopped working within a few hours, while it lasted up to seven hours in other patients.

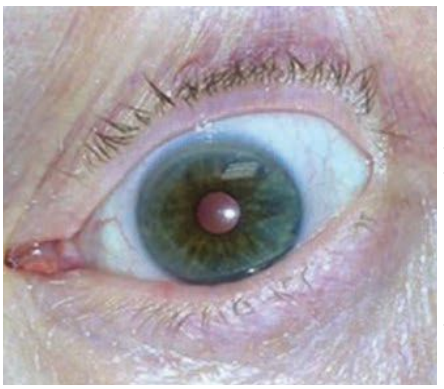


Photo: Michael Trottini, OD, and Michael DelGiodice, OD

Pupil constriction following (therapeutic) pilocarpine use. ODs are familiar with previous incarnations of the drug after decades of medical use prior to its FDA approval for presbyopia.

The unpredictable duration could be a deterrent for some patients, especially those whose workday is eight hours or longer. This may mean that contact lenses or glasses might still make the most sense as a primary corrective modality, at least during the work week. Given Vuity's newness as of this writing, the profession has yet to develop even anecdotal impressions of the implications for usage beyond the FDA recommended dosage of one drop in each eye once daily.

Still, the general consensus appears to be that Vuity should be explored and embraced as a new avenue of treatment for some well-chosen and appropriately educated patients. Prepping the patient is key and, as always, it is important to share all available options while being mindful to thoroughly explain the pros and cons of each.

For Paymaun Asnaashari, OD, of Helmus Optometry in Sacramento, CA, the patients he has successfully prescribed Vuity for are the ones who come to their exam already interested in hearing more about this approach. People who are learning about it for the first time from him are harder to convince. "I have brought this treatment up to multiple patients, especially the presbyopes who are starting to lose their ability to read, and, so far, many are hesitant to try it," he explains.

According to Dr. Asnaashari, one point of resistance for his patients has been the cost. Currently, Vuity is not covered by insurance and, at $80 per 30-day supply, can be a significant out-of-pocket expense. If patients and practitioners begin to develop off-label protocols that involve more frequent dosing than QD to extend the drug's effect, the cost proposition obviously worsens as a consequence. Being upfront with your patients about the cost and other potential cons is key, he suggests.

While Dr. Shovlin doesn't think cost will be a significant barrier to use overall, he does have some concerns that the price tag could prompt individuals to attempt to obtain pilocarpine 1%. "I have heard that already some areas of the country have limited stock of generic pilocarpine for other uses," he says. "It's important to remind our patients and colleagues that this is the same drug but not the same compound, since Vuity has a unique vehicle and formulation."

Another important topic is correct usage and timing. Dr. Shovlin says patients should exercise caution early on while driving until they've gauged their comfort. Dr. Barnett adds that contact lens wearers should be advised to instill the drops first, then apply their contact lenses 15 minutes later.

Additionally, make time to have a discussion with your patients prior to anticipated dilation so they can stop using the drop a few days prior, according to Dr. Shovlin, who acknowledges that this could be a challenge for patients who present with acute symptoms of retinal pathology, such as flashes, floaters, specks and cobwebs.

"I do have some reservations in patients who might use something like this for years prior to cataract surgery and may not get adequate dilation for their cataract removal," notes Dr. Shovlin. "If prescribing recommendations continue to highlight age 55 as the cutoff, this shouldn't pose a major problem."

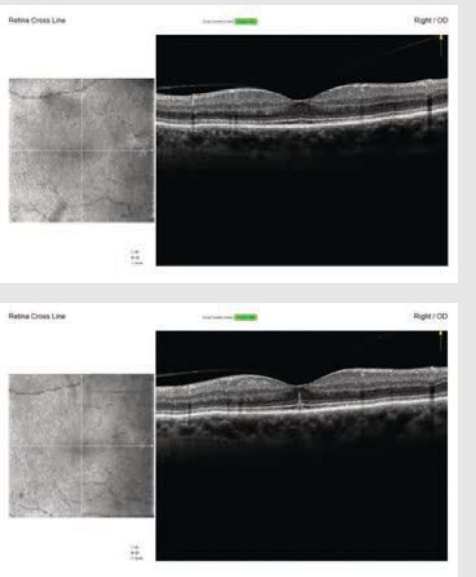
ONE OPTOMETRIST'S CAUTIONARY TALE

When she first received an inquiry about Vuity, Susan Caul, OD, who practices in Redwood City, CA, decided to try the drug herself before prescribing it to any of her patients.

On the morning of February 6, she instilled one drop in each eye. About 10 to 15 minutes later, she recalls her right eye starting to develop a central pixelated-like spot that progressed to a brown dusty spot and then a central blur. She reached out to two retina specialists she refers to who advised her to wait it out, as the side effects would most likely resolve when the drop wore off.

Six to eight hours later, the scotoma had shrunk but not resolved. She went to her office the next morning for a macular OCT, which showed a subfoveal outer retinal disruption. Her corrected acuity had dropped from 20/20 to 20/25, and she had a small central scotoma that obscured about half of the number or letter that she was looking at.

Two weeks later, the scotoma had still not fully resolved. Follow-up OCT every few days showed the disruption to be shifting slightly in shape, but her visual disturbance was unchanged. "I have not had a posterior vitreous detachment in this eye, but I had one in my fellow eye in 2019," she explains. "I did a literature search and found a similar case with administration of pilocarpine 2%. The mechanism was presumed to be vitreofoveal traction due to a forward displacement of the lens."[1]



OCT scans of Dr. Caul's right eye taken before (June 2021, top image) and after (February 2022, bottom image) her adverse event.

Regarding her near vision status post-Vuity, Dr. Caul says she still needed to use her reading glasses to see print. "It was hard to tell if there was any improvement in my near visual acuity, and my visual disturbance clouded any near visual acuity benefit that may have occurred," she notes. "I also experienced a sort of 'jiggling' in my vision as though I had nystagmus in the first 30 minutes after installation only when I used my computer."

Based on her personal experience, she says, "Although pilocarpine was used for years as a glaucoma treatment and this drop was approved by the FDA for presbyopia, there are potential side effects that could possibly be serious. Anyone prescribing this needs to be aware of potential risks and make sure the patient is informed."

1. Walker JD, Alvarez MM. Vitreofoveal traction associated with the use of pilocarpine to reverse mydriasis. Eye. 2007;21:1430-1.

While serious adverse events are exceedingly rare, ODs should remain aware of issues such as iris cysts, angle widening resulting in closure, accommodative spasm and retinal detachment in myopes, Dr. Shovlin advises.

As with any therapeutic option, it is up to the optometrist to inform their patients of the risks vs. benefits, as well as to help them determine if this treatment makes sense for their individual needs. "The drug is readily available and easy to administer with fast onset and sufficient duration. Patients will know pretty early on whether this drop makes sense for them," says Dr. Shovlin. "Overall, the response has been favorable for those who are properly screened and have had an adequate education on how to best use the drop."

Implications For Optometric Practice

In addition to offering presbyopic patients another option, Vuity can also

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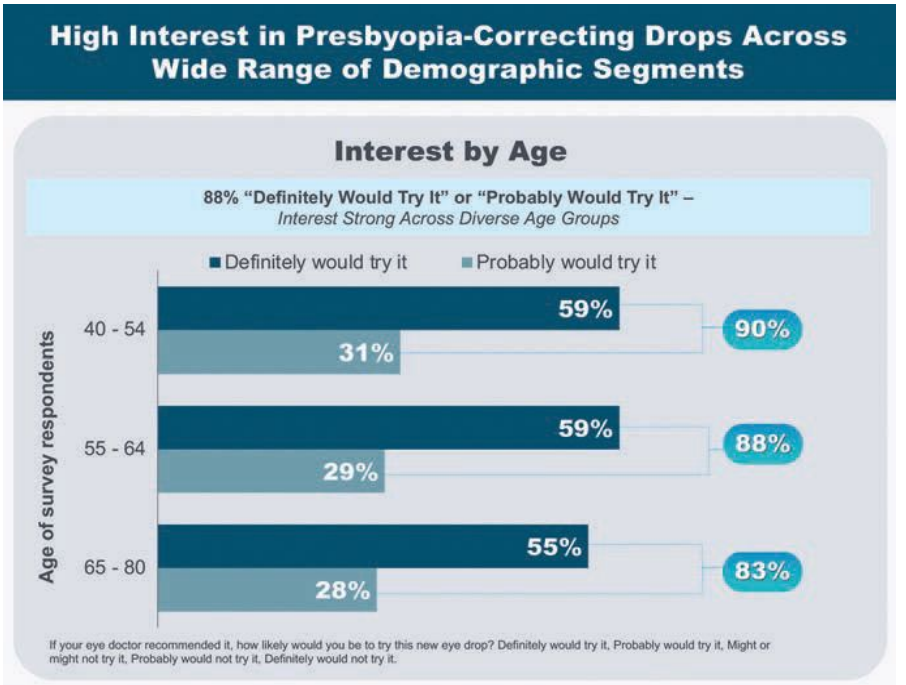

As part of her AAO 2021 presentation, Dr. Barnett shared patient motivations and expectations surrounding presbyopia-correcting drops.

be a source of added value for optometrists and their practice. "A doctor who presents a comprehensive range of options is recognized and appreciated by their patients," Dr. Bazan notes. "It helps solidify the doctor as an expert in solving the visual needs of a patient and strengthen the doctor-patient relationship."

"Patients often have doctors who are passive in their approach, failing to present innovations in the industry that really can help optimize a patient's visual experience," Dr. Bazan emphasizes. "They have bad habits of waiting for a patient to bring it up. Patients with proactive doctors are rewarded with options that often enhance vision and improve their lifestyle. Vuity is a great example of this."

The availability of this treatment has the potential to attract not only new patients but also those who may not be visiting their eye doctor as often as they should. "We have the opportunity to provide eye care for more patients, many of whom have not received it before, such as emmetropic presbyopes," notes Dr. Barnett. "More than one-third of presbyopic emmetropes have either never seen an eye doctor or have seen one as rarely as every four years. Additionally, 31 million Americans use over-the-counter reading glasses. The approval of a pharmaceutical option for presbyopia is a huge opportunity for eye care and eye care providers to provide eye examinations to diagnose ocular and systemic disease."

The Next Wave of Therapeutics

With other pharmaceutical agents on the horizon for presbyopia, the introduction of Vuity offers a first look at the potential impact of this approach. Time—and further research—will reveal what is possible and if these innovations will change the way optometrists manage presbyopic patients.

Some manufacturers are using cholinergic muscarinic agonists such as pilocarpine in combination with novel ingredients. According to Dr. Shovlin, these new compounds may be effective in enhancing accommodation and depth-of-focus.

Eyenovia has a pilocarpine eye drop in development, with one Phase III study completed and another underway. Additionally, Orasis Pharma has initiated a Phase III clinical trial of its drug CSF-1, which combines pilocarpine and a lubricant.[5]

"I am aware of at least six other compounds that produce miosis. Most are in the Phase III FDA approval process," notes Dr. Shovlin. "Lenz Therapeutics is studying the use of aceclidine and Visus Therapeutics is using combined carbachol/brimonidine for a possible dual/synergistic action."

For a non-miotic approach, Novartis has a lipoic acid/choline ester compound in devemopment, adds Dr. Shovlin. "This drug has been designed to increase accommodation ability," he explains. "The prodrug reduces dihydrolipoic acid within the lens fibers, causing hydrolysis of the disulfide protein bonds and restoring lens elasticity."

As this field continues to grow, optometrists are perfectly positioned to educate patients and usher them into a new era of presbyopic treatment. "With the ongoing evolution and advancement of medicine, it is important to be a leader for your patients. It is our responsibility to inform them of every option and help them understand what is available," notes Dr. Asnaashari. "As with any new innovation, there is a learning curve, but the potential impact is significant. It is truly an exciting time to be an optometrist, and I look forward to what comes next." ■

1. First presbyopia eye drop approved. Review of Optometry. October 29, 2021. www.reviewofoptometry.com/article/first-presbyopia-eye-drop-approved. Accessed February 27, 2022.

2. Efficacy study of pilocarpine HCl ophthalmic solution (AGN-190584) in participants with presbyopia (GEMINI 1). ClinicalTrials.gov. clinicaltrials.gov/ct2/show/results/NCT03804268. Accessed February 27, 2022.

3. A phase 3 efficacy study of pilocarpine HCl ophthalmic solution (AGN-190584) in participants with presbyopia (GEMINI 2). ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT03857542. Accessed February 27, 2022.

4. U.S. Food and Drug Administration approves Vuity (pilocarpine HCl ophthalmic solution) 1.25%, the first and only eye drop to treat presbyopia (age-related blurry near vision). Abbvie. October 29, 2021. news.abbvie.com/news/press-releases/us-food-and-drug-administration-approves-vuity-pilocarpine-hci-ophthalmic-solution-125-first-and-only-eye-drop-to-treat-presbyopia-age-related-blurry-near-vision.htm. Accessed February 27, 2022.

5. An evaluation of the efficacy and safety of CSF-1 in the temporary correction of presbyopia (NEAR-1). ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT04599933?term=orasis&draw=2&rank=3. Accessed February 27, 2022.

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Reference: 1. Chang W-H, Liu P-Y, Lin M-h, et al. Applications of hyaluronic acid in ophthalmology and contact lenses. *Molecules.* 2021;26:2485

VTI REDEFINING VISION

FIVE COMMON DRUG Rx QUESTIONS—ANSWERED!

Gain confidence in your ability to prescribe with these tips for managing a variety of patients, from those on oral steroids to those with penicillin allergy.

BY JESSICA STEEN, OD
FORT LAUDERDALE, FL

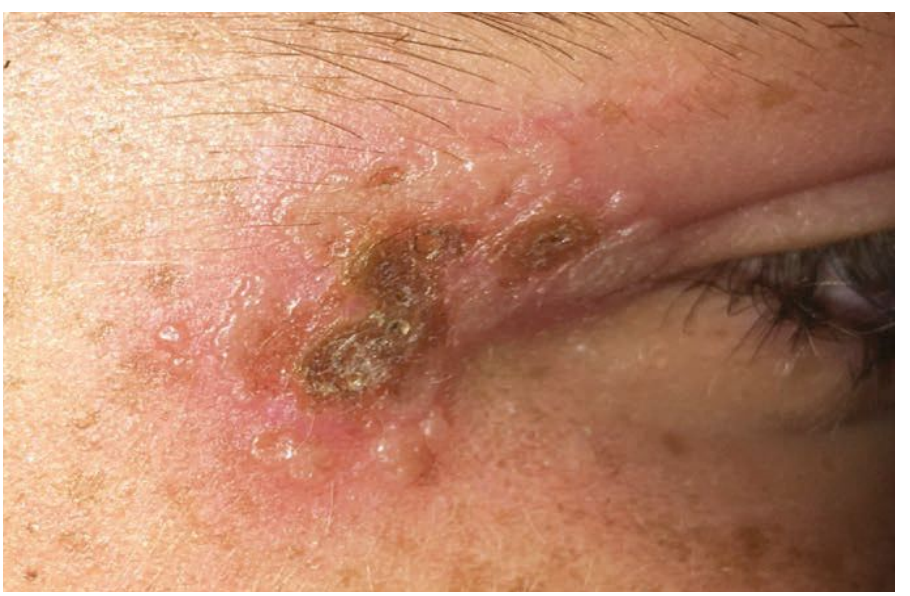
With the continued move to medical models of care delivery and the increased scope of optometric practice across the country and the world, it is more important than ever that optometrists be well-educated on prescribing therapeutics for ocular disease.

There are many nuances to safe and effective prescribing of oral medications in adult and pediatric populations for infectious and inflammatory conditions. Maximizing treatment success requires a careful understanding of pathophysiology, individual patient characteristics, known patterns of resistance, pharmacokinetics, insurance coverage and availability of medications.

Here, I will address some of the most frequently asked prescribing questions in clinical practice and update you on the latest guidelines for treating various types of patients with a variety of oral medications.

1. Oral antiviral agents: are they all the same?

The shift in prescribing away from topical antiviral agents in the setting of herpes simplex epithelial keratitis to oral agents reflects the efficacy, safety and availability of these agents in the United States.[1] In treating herpes zoster and herpes simplex ophthalmic infections, prescribers have options when it comes to choosing an oral antiviral agent. Famciclovir, acyclovir and valacyclovir are all available as branded and generic products, are all effective and all have an excellent margin of safety for the majority of individuals requiring treatment of ocular infections due to herpes simplex and varicella zoster virus.[1-6] Common adverse effects



Primary ocular herpes simplex infection may manifest as blepharitis.

About the author

Dr. Steen is an attending optometrist and assistant professor at Nova Southeastern University College of Optometry. She has no financial interests to disclose.

TABLE 1. ORAL ANTIVIRAL DOSING SUMMARY[1,3-6]

	VZV	Active HSV: therapeutic dose (dendritic epithelial keratitis)	HSV prophylaxis: stromal keratitis without epithelial ulceration
Famciclovir	500mg TID x 7-10 days	250mg BID-TID x 7-10 days	250mg BID
Acyclovir	800mg 5x/day x 7-10 days	400mg 3-5x/day x 7-10 days	400mg BID
Valacyclovir	1g TID x 7-10 days	500mg BID or 500mg TID x 7-10 days	500mg QD

include headache and nausea.[1] All oral antiviral medications are cleared through the renal system, and renal dysfunction is known to be a rare but serious potential adverse effect. Individuals should be advised to drink plenty of water while undergoing therapy to reduce the likelihood of such adverse effects. In addition, individualized dosing adjustments must be made for individuals with reduced renal insufficiency or failure based on creatinine clearance.[1]

Considering the approximate equivalency in clinical efficacy, prescriber preference of agent is generally based on dosing frequency, cost and availability (*Table 1*). Valacyclovir is a prodrug of acyclovir. Due to the improved oral absorption and bioavailability of valacyclovir compared to acyclovir, it has a less onerous dosing strategy and is therefore typically the oral antiviral of choice in treating herpes simplex virus (HSV) ophthalmic infections and herpes zoster ophthalmicus. While both drugs are on-label to treat herpetic viral infections in individuals two years of age and older, the safety of valacyclovir has been evaluated in individuals as young as one month old and is typically considered the pediatric antiviral agent of choice by physician.[3,4]

Famciclovir is the oral prodrug of penciclovir, which has a different mechanism of antiviral activity than acyclovir but is also effective for the treatment of herpes simplex virus and herpes zoster virus (HZV) with similar efficacy in individuals 18 years and older.[1,2,5]

Dose and dosing strategy for treatment of HSV-associated anterior segment conditions varies by clinical diagnosis due to the underlying differences in pathogenesis. The dosage for the treatment of varicella zoster virus, the cause of HZV, is at least twice that of the dosage for herpes simplex epithelial keratitis, depending on the agent.[6] Herpes simplex keratitis exists along a spectrum of clinical presentation, and dosing strategy and frequency of administration of oral agents may vary based on physician preference.

Emerging resistance of strains of HSV-1 to acyclovir should be considered in immunocompromised individuals, especially in those who have had long treatment courses—generally associated with prophylaxis.[7] Unfortunately, most acyclovir-resistant HSV isolates are cross-resistant to penciclovir; however, resistant strains may be treated with intravenous Foscarnet (brand name: Foscavir).[1]

2. My patient has a penicillin allergy, now what?

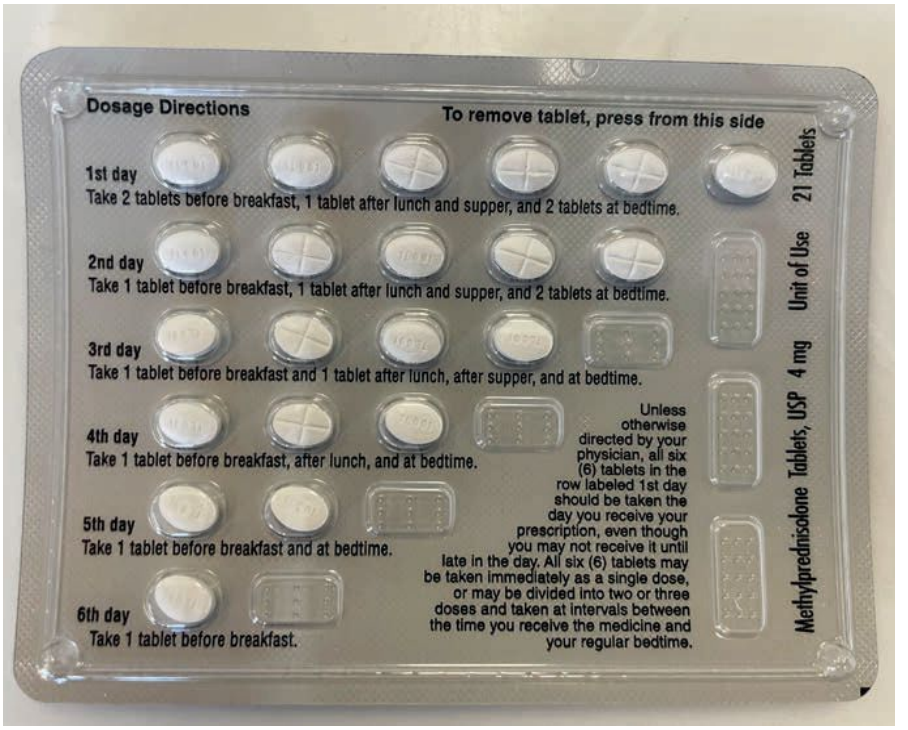
While 10% of the population reports having a penicillin allergy, prevalence data of true Type 1 immunoglobulin E (IgE)-mediated response to penicillin suggests only about 1% of the population is truly allergic.[8] When a patient reports a history of penicillin allergy, a careful history should be taken to understand the medication responsible for the reaction, the kind of reaction, how the reaction was managed and the outcome following the reaction.[9,10] Penicillin skin testing should be performed to confirm or rule out penicillin allergy in conjunction with the patient's allergist or managing physician, which may not be practical in settings requiring acute treatment.[9,10] Patients with a true penicillin allergy or IgE-mediated reaction may report symptoms including shortness of breath, wheezing, hives, angioedema and anaphylaxis, which occur immediately or within approximately an hour after exposure to the medication.[8-10]

Cephalosporins can be considered in patients with penicillin allergy due to the low potential for cross-reactivity, approximately 2%.[10] While the risk of cross-reactivity lessens with later-generation cephalosporins, one commonly used in clinical practice, cephalexin, is a first-generation cephalosporin. The risk of cephalosporin use should be carefully weighed against the potential benefit in these individuals, especially those with history of severe reaction, such as anaphylaxis to penicillin.[8,10]

In an individual with penicillin allergy, asking them about their successful experience with other antibiotics can help to guide the discussion regarding the risks and benefits of alternative antibiotics including sulfamethoxazole/trimethoprim, azithromycin and doxycycline. Knowing a patient's medication history is the key to choosing a medication that

Photo: Randall Thomas, OD

For patients with a penicillin allergy, cephalosporins could be considered as an alternative treatment option. However, it's important to gather as much data as possible about the patient and his or her allergy to make an informed choice of an alternative antibiotic to prescribe.



A methylprednisolone 4mg dose pack with incorporated dosage directions, which can be prescribed to help reduce risk of adrenal insufficiency in patients tapering off steroids.

will give them the least amount of side effects and the best chance for a positive outcome.

It's important to note that oral fluoroquinolones are rarely prescribed in eye care and have been advised to be reserved for circumstances where no other treatment options exist through the FDA due to their generally unfavorable risk-benefit ratio.[11]

3. Oral steroids: when is tapering necessary?

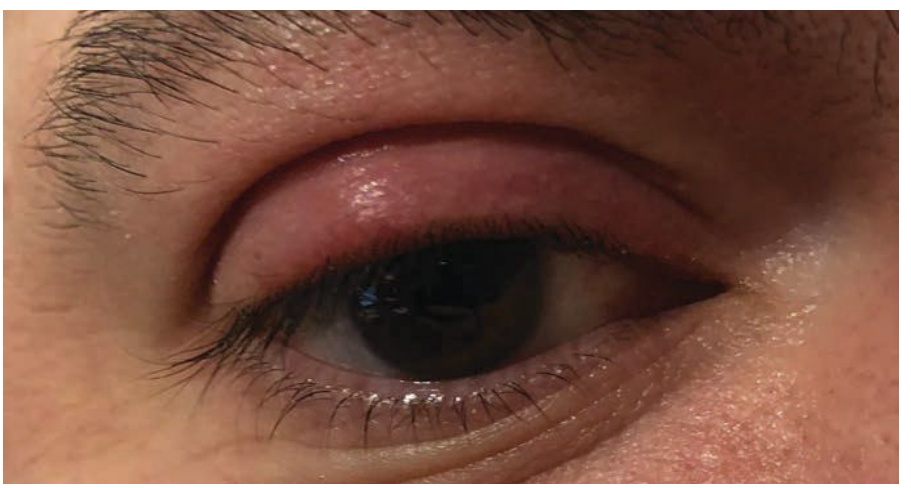
Management of acute inflammatory episodes, such as exacerbation of peripheral ulcerative keratitis or thyroid orbitopathy, differ greatly from the management of conditions that require high dose, long-term immune suppression, like giant cell arteritis, due to inherent differences in underlying pathophysiology.[12]

In general, as the dosage or the duration of systemic steroid therapy increases, so does the risk of systemic adverse effects including adrenal insufficiency and potential for glucocorticoid withdrawal syndrome. Therefore, prescribers often aim to treat with the lowest dosage of systemic steroid for the shortest period of time possible while reaching the required clinical effect.[13]

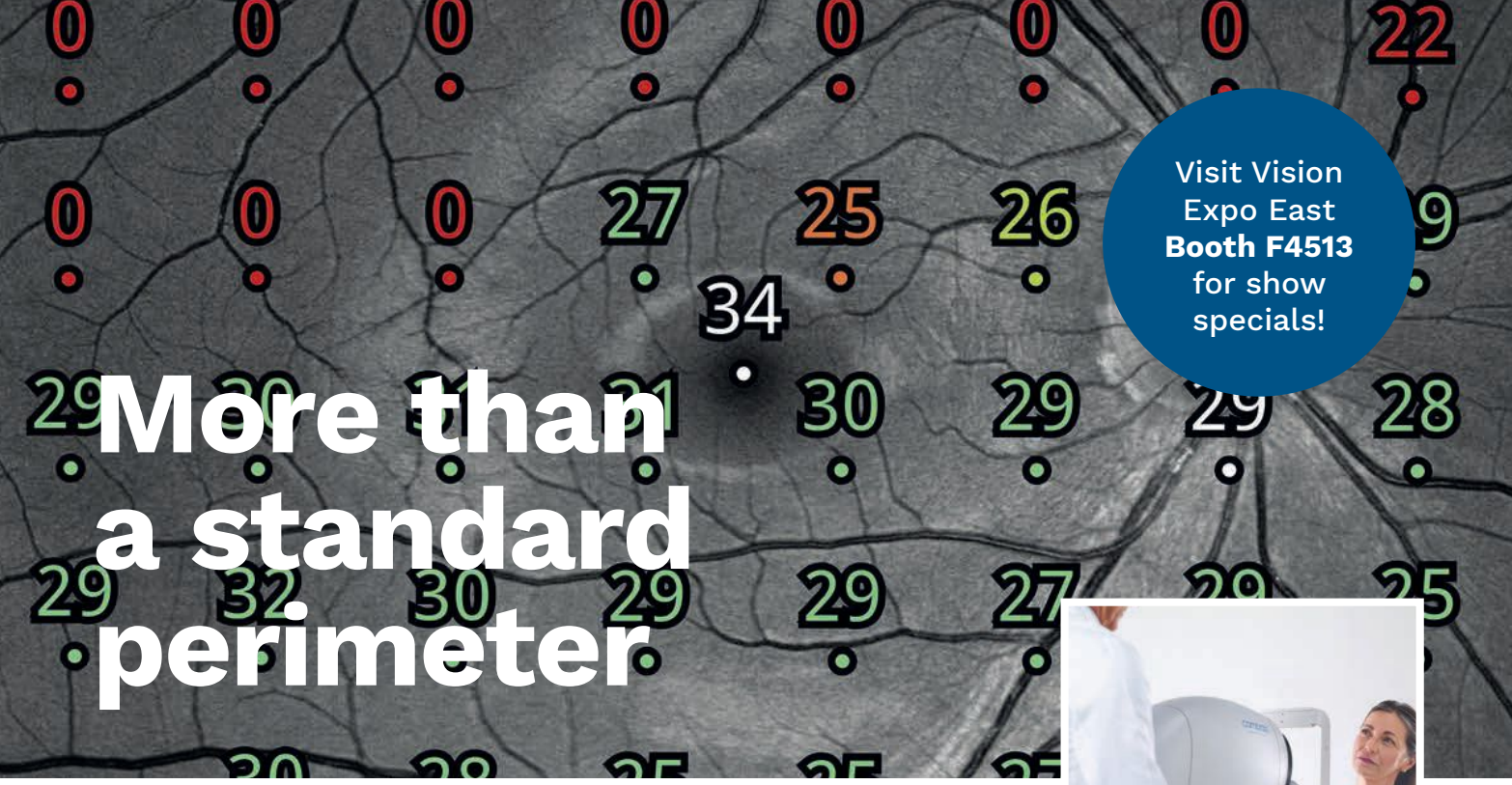
Oral corticosteroids like prednisone, prednisolone and methylprednisolone mimic glucocorticoids produced in the adrenal cortex. Endogenous corticosteroid production is equivalent to about 5mg to 7.5mg of prednisolone daily.[13] Physiological corticosteroid production is downregulated when exogenous steroids are present due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Tapering systemic steroids allows the HPA axis to gradually adjust to the exogenous steroid withdrawal to signal a return of adrenal gland function and increased cortisol production back to physiologic levels while ensuring the underlying disease process remains suppressed.[13,14]

The rate at which tapering occurs is based on the condition being treated and the duration of treatment. While every clinician has a personal preference when it comes to taper pattern, for patients taking greater than 40mg of prednisolone or an equivalent dosage for more than seven days, a reasonable approach involves decreasing the daily dosage by 5mg to 10mg in weekly increments until 20mg of prednisolone or equivalent is reached, followed by a slow taper of 1mg to 2.5mg weekly until 5mg daily is reached. This slow, sustained taper allows natural cortisol levels to gradually return to a normal range.[13,14]

Tapering steroids too quickly may cause adrenal insufficiency, resulting in symptoms including headache, fatigue, joint and muscle pain, weight loss, hypoglycemia and fever, which may range from mild to life-threatening.[13,14] In addition to a slow taper



This patient has an internally-pointed hordeolum of the upper eyelid, a finding commonly associated with MRSA infection.



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and minimizing the overall steroid load, to reduce the likelihood of adrenal insufficiency, steroids should be dosed in the morning with as few split doses as possible to mimic circadian adrenocorticotropic hormone release.[13]

Traditionally, steroid taper is recommended following a treatment with the equivalent of 40mg of prednisolone or greater for more than seven days; however, as adrenal suppression and resulting insufficiency can occur rapidly following the initiation of even low dosages of systemic steroids, a short taper may be included in your indications for use, even for short-term steroid pulses.[13,14] A commercially available pre-packaged methylprednisolone dose pack incorporates a pulse followed by a gradual reduction in the steroid over a six-day treatment period, which aids in medication adherence and helps minimize risk of adrenal insufficiency.[12]

4. Which antibiotics are effective against MRSA?

While methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been on the decline in the United States from the mid-2000s, the infection and associated multi-drug resistance continue to be responsible for significant morbidity and mortality and are a common cause of periocular soft tissue infection.[15-17] Consider the potential for MRSA as a causative organism for individuals who present with periorbital infections and identify as one of the following: patients who work in healthcare environments or were recently hospitalized or incarcerated, athletes, patients with a history of MRSA or who share a living environment with those with a previously diagnosed MRSA infection and those who have non-resolving infections who have been previously treated with a penicillin, cephalosporin or macrolide.[15,17]

Based on known resistance patterns of MRSA in the United States, commonly prescribed oral antibiotic agents in eye care, specifically: penicillins, cephalosporins, and azithromycin, have limited-to-no antimicrobial effect against MRSA.[16] Based on individual characteristics and overall individualized risk assessment, while these antibiotics may still be a preferred first-line agent of choice for soft tissue infection, consider the potential for resistance, monitor these patients frequently and adjust the treatment strategy accordingly when limited clinical improvement is observed.

For treatment of suspected MRSA infection, one tablet of sulfamethoxazole and trimethoprim DS containing 800mg of sulfamethoxazole and 160mg of trimethoprim twice daily is the treatment of choice in the absence of sulfonamide antibiotic allergy for most adult patients.[16,18] Clindamycin 300mg three times daily or doxycycline 100mg twice daily with food can also be considered when clinically appropriate.[16,19,20] A careful risk-benefit evaluation should be performed and discussed with the patient prior to prescription of any oral medication. While all antibiotics alter natural colon flora, clindamycin carries a specific black box warning of *Clostridium* difficile-associated diarrhea, the development or overgrowth of a severe antibiotic-resistant strain of microbe which may lead to fatal colitis.[19]

Amoxicillin and clavulanate potassium tablets are commonly prescribed to children and typically dosed based on weight.

The amount of time to resolution of infections varies, so adjust the follow-up schedule accordingly to optimize the course of treatment based on clinical improvement and resolution of the condition. While some patients may have complete resolution within five days of treatment, others may require 10 or more days.[21] Treatment optimization helps limit the overuse of antibiotics.[21]

Most MRSA strains are susceptible to vancomycin; however, this medication's use is uncommon in an outpatient setting due to the need for intravenous administration, as well as the concern for judicious use of vancomycin in clinical settings to attempt to delay development of resistance.[16]

5. Antibiotics in kids—what's the right dosage and concentration?

Prescribing oral medications for pediatric patients requires an understanding of relevant data regarding the proposed antibiotic, potentially causative pathogen of the infection and individual patient characteristics. While dosage and concentration of medications is often based on patient weight, we know that significant variation in physiological maturation between individuals of the same weight is common, which can result in discrepancies from intended effective dosage resulting in undertreatment, or more likely, increased risk of adverse effects due to overtreatment.[22]

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ADVERSE REACTIONS: Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

Please see the Full Prescribing Information on the next page.

Reference: 1. Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol.* 1984;16(12):1110-1115.

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Shake Well Before Using. One to two drops instilled into the conjunctival sac(s) four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to two drops every two hours. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

CONTRAINDICATIONS
Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

WARNINGS AND PRECAUTIONS
Topical Ophthalmic Use Only
For topical ophthalmic use only. Not for injection.

Intraocular Pressure Increase
Prolonged use may result in glaucoma, damage to the optic nerve, and defects in visual acuity and visual field. It is advisable that the intraocular pressure be checked frequently.

Cataracts
Use of corticosteroids may result in cataract formation.

Delayed Healing
Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids.

Viral Infections
Use in the treatment of herpes simplex infection requires great caution.

Bacterial Infections
Use of corticosteroids may suppress the host response and thus aid in the establishment of secondary ocular infections. Acute purulent infections of the eye may be masked or exacerbated by the presence of steroid medication.

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

Contamination
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Contact Lens Wear
Contact lenses should be removed during instillation of FLAREX but may be reinserted after 15 minutes.

Temporarily Blurred Vision
Vision may be temporarily blurred following dosing with FLAREX. Care should be exercised in operating machinery or driving a motor vehicle.

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Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

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The following reaction has been identified during postmarketing use of FLAREX in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes dysgeusia.

USE IN SPECIFIC POPULATIONS
Pregnancy
Fluorometholone has been shown to be embryocidal and teratogenic in rabbits when administered at low multiples of the human ocular dose. Fluorometholone was applied ocularly to rabbits daily on days 6-18 of gestation, and dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs, and neural abnormalities, such as encephalocele, craniorachischisis, and spina bifida, were observed. There are no adequate and well-controlled studies of fluorometholone in pregnant women, and it is not known whether fluorometholone can cause fetal harm when administered to a pregnant woman. Fluorometholone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLAREX is administered to a nursing woman.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

PATIENT COUNSELING INFORMATION
Risk of Contamination
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Use with Contact Lenses
The preservative in FLAREX, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX but may be reinserted 15 minutes after instillation.

Temporarily Blurred Vision
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adverse effects so the prescribed dosage may be reevaluated.

The most precise prescribing information comes from the package insert of the proposed medication, which is accessible online through the Drugs@FDA: FDA-Approved Drugs webpage.[23]

Pediatric dosing calculations are always in metric measurements and usually described in milligrams of medication per kilogram of patient weight (mg/kg). A maximum daily dosage will also be included for pediatric dosing, which prescribers should pay careful attention to, especially when prescribing medications for obese children.[22]

Let's take a look at an example of a commonly prescribed oral antibiotic in pediatrics: amoxicillin/clavulanic acid. The oral dosage, based on the amoxicillin component for children between three months of age and who weigh 40kg, is 25mg to 45mg/kg/day. The oral suspension is available in four concentrations of the amoxicillin component and two different dosing strategies: 200mg/5mL and 400mg/5mL, dosed every 12 hours, and 125mg/5mL and 250mg/5mL, dosed every eight hours. A 12-hour dosing regimen is typically preferred due to significantly less associated diarrhea.

For a patient with a mild infection, 25mg/kg/day is an appropriate dosage, and for an individual with a more severe infection, 45mg/kg/day of amoxicillin should be considered. For a five-year-old who weighs 20kg with a mild periorbital soft tissue infection, a dosage of 25mg/kg/day every 12 hours calculates to 500mg of amoxicillin daily (with 125mg clavulanic acid), or 250mg twice daily. As each teaspoon (5mL) contains 200mg of amoxicillin, the total daily dosage is 2.5 teaspoons (12.5mL) or 1.25 teaspoons (6.25mL) every 12 hours. When prescribing, keep in mind that oral suspensions need to be shaken well.[24]

Pediatric prescribing errors are unfortunately common due to the process of multi-step calculations that consider the weight of the individual, dosage of the medication, concentration of the medication and dosing interval. Errors based on weight—where weight may be measured, recorded or communicated incorrectly—are also a frequent cause of prescribing errors.

> **Pediatric prescribing errors are unfortunately common, due to the multi-step calculations that consider weight, dosage, concentration and interval.**

It may sound obvious, but it's important to always double-check calculations to limit prescription errors because the risk of miscalculating a dosage is just too high. App-based pediatric dosing calculators, which one can simply download on their smartphone, may also be useful and can minimize mathematical errors.[24]

The Bottom Line

Nuances in prescribing oral medications take into account a wide variety of ophthalmic condition-, medication- and patient-specific factors. Patient outcomes, as well as their satisfaction with the quality of care they receive, rely on the accuracy of a physician's treatment and prescribing recommendations. Optimizing medical therapy requires the understanding of the latest available options and careful evaluation and communication of potential risks and benefits to maximize treatment success. ■

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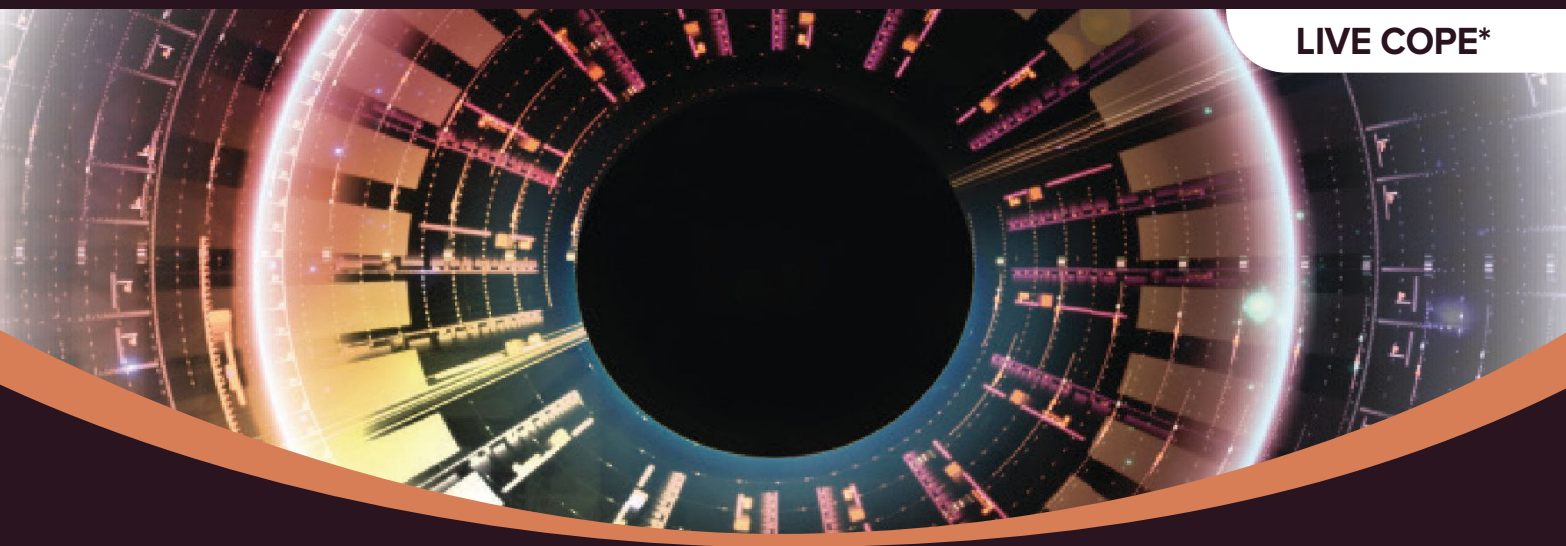

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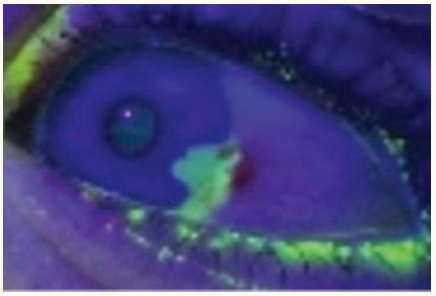
MANAGING PEDIATRIC OCULAR PATHOLOGY

Safe treatment of these patients requires a comprehensive understanding of available therapeutics.

BY AMY WATERS, OD
KANSAS CITY, MO

Children often present unique yet rewarding challenges when it comes to prescribing medications for ocular pathology. Drugs that are used in adults may sometimes be contraindicated in children or not approved for use at all in this patient population. The dosage of oral medications is also very different in children compared with adults. While many classes of ophthalmic medications have information for pediatric use, it is estimated that over 80% of all medications that have been approved in adults do not have information for pediatric use.

The research on drug safety in children has seen improvements over time. The Best Pharmaceuticals for Children Act (BPCA) of 2007 allows for six months of marketing exclusivity if children are included in the research for the new drug. The Pediatric Research Equity Act can require pediatric research into new drugs under certain circumstances.[1]



Corneal and conjunctival abrasion with subconjunctival hemorrhage. A Burton/Woods lamp is beneficial for visualization in infants and toddlers.

When ocular pathology strikes, what drugs and dosages can we use for the pediatric patient population? This article will review common anterior segment conditions, as well as the topical and oral medications used to treat them in children. It will provide the necessary tools to safely manage pediatric ocular pathology using available therapeutic interventions.

Conjunctivitis

Both bacterial and viral conjunctivitis are relatively common in pediatric patients; therefore, optometrists should remain aware of how to best manage these conditions.

Bacterial conjunctivitis. This condition is usually self-limiting, but treatment can decrease its course, prevent the spread of infection and cause children to be able to return to school more quickly. For these reasons, bacterial conjunctivitis in children is most often treated with topical antibiotics. Cultures are typically not obtained and are usually not necessary. However, suspected neonatal conjunctivitis is an emergency and requires cultures and potential hospitalization. Most eye drops require a five- to seven-day course and are dosed three to four times daily. Many antibiotic ophthalmic drops include prescribing information for children. The majority are dosed the same as in adult patients.

A recent study on bacterial conjunctivitis found that one in four

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cases were polybacterial. A broad-spectrum antibiotic is warranted in pediatric bacterial conjunctivitis.[2,3] Moxifloxacin hydrochloride (Moxeza, Alcon/Novartis; Vigamox, Alcon and A-S Medication Solutions) has been approved for all age ranges and is typically well tolerated. The dosage is one drop three times daily for seven days.[4] Trimethoprim/polymyxin B sulfate is also approved in children over two months of age but needs to be administered more frequently. The recommended dosage is one drop every three hours, not to exceed six drops per day for seven to 10 days.[5] The most common cause for bacterial conjunctivitis in young children is *Haemophilus influenza*, which has also been noted to cause otitis media. In a child with a concurrent ear infection and red eye, bacterial conjunctivitis should be considered.[6]

Viral conjunctivitis. The hallmark sign of this condition is a follicular response on the conjunctiva with a red, watery eye. There is currently no well tolerated treatment for viral conjunctivitis in young pediatric patients, as they are not very tolerant to povidone-iodine treatments that have been described to treat adult viral conjunctivitis off-label. Supportive therapy such as cold compresses and artificial tears are the primary treatment. If there is significant discomfort for the child, consider a treatment with an antibiotic/steroid combination or a topical steroid. If there are significant corneal infiltrates, treat this with a topical steroid; however, this therapy option should be reserved for more severe cases. If topical steroids are pursued, a softer steroid such as loteprednol etabonate (Alrex, Bausch + Lomb; Lotemax, Bausch + Lomb; Eysuvis, Kala Pharmaceuticals) or fluorometholone is preferred since there is not a need for deep penetration into the eye and because these medications are less likely to cause elevation of IOP.[7]

Since the signs and symptoms of different types of conjunctivitis can overlap in cases of acute red eye, an in-office rapid test can evaluate whether the infection is adenovirus. This does not rule out all causes of viral conjunctivitis but can be especially helpful in deciding on treatment if there is a positive result.[8]

Pediatric Trauma

Children commonly present with ocular trauma. Those with closed globe injuries typically respond quite well to treatment. One difficulty that arises with pediatric trauma is that injuries are sometimes not witnessed by adults and history may be limited. The clinician may also not get a complete history because the patient is more hesitant to offer details. In all cases of blunt or unwitnessed trauma, a complete dilated eye exam is indicated.

A pediatric corneal abrasion is treated slightly different in this young population than in adults. In young children, bandage contact lenses are not as easily placed or removed. A Cochrane review did not find sufficient evidence of benefit with this therapy and recommended more research into the topic.[9] If a pediatric patient is unable to keep their hands away from their eyes and the abrasion is worsening—or not improving—a pressure patch can be considered. However, the patient should be managed closely due to the increased risk of microbial infection. Bandage contact lenses should be considered if a patient is old enough to tolerate insertion and removal.

Topical antibiotics include moxifloxacin hydrochloride drops, erythromycin ointment, trimethoprim/polymyxin B sulfate drops and ciprofloxacin hydrochloride ointment. Ointment tends to provide better relief after corneal abrasions and is sometimes easier to instill in children after injuries. Ointment is typically prescribed to be used three to four times daily. Educate caregivers that these treatments should be used prior to naptime and bedtime.

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Faculty/Editorial Board: Amy Waters, OD

Educational Objectives: After completing this activity, the participant should be better able to:

- Appraise how to treat pediatric ocular pathologies.
- Identify which drugs are approved for what ages.
- Select the right medication and dosage for various conditions.
- Describe strategies to minimize adverse effects when treating pediatric patients.

Target Audience: This activity is intended for optometrists engaged in managing pediatric patients.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by PIM and the Review Education Group. PIM is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council for Pharmacy Education and the American Nurses Credentialing Center to provide CE for the healthcare team. PIM is accredited by COPE to provide CE to optometrists.

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Patient with active BKC, peripheral corneal infiltrates and capped meibomian glands.

Hyphema, which is also more common in children, can occur with blunt trauma and commonly happens because of sports injuries.[10] Due to the lack of availability of homatropine, first-line treatments include cyclopentolate 1% twice daily or atropine 1% once daily with a topical steroid. Prednisolone acetate (Pred Forte, Allergan; Pred Mild, Allergan) should be dosed QID. Once the hyphema is resolved, the cycloplegic agent is discontinued and the steroid drop is tapered.

Patients need to be followed very closely the first 48 hours and closely until the hyphema resolves, especially in cases of elevated IOP. Encourage bedrest, with a head elevation of 45° and no NSAIDS, as this can increase the risk of rebleed. Patients and parents should be educated on the short- and long-term risk of glaucoma after hyphema. Risk of rebleed is highest in the first two to five days after injury. The patient should also be thoroughly evaluated for other ocular injuries.[10]

Sickle cell disease with hyphema carries a much greater risk of increased IOP and secondary complications due to the sickling of red blood cells in the trabecular meshwork. Inquire about a history of African or Middle Eastern decent. If sickle cell status is unknown in an at-risk population, screen the patient for sickle cell disease. Atropine is typically contraindicated in patients with a heart disorder, so it is important to obtain medical history including any cardiac problems. Discussions with the patient's cardiologist or primary care physician may be indicated to weigh risks and benefits of treatment in those with a positive cardiac history.

If IOP rises during the treatment of hyphema, there are multiple medications to consider. Dorzolamide hydrochloride/timolol maleate is a good first-line medication combination if the patient does not have a history of asthma or other contraindications. Alpha-2 adrenergic agonists have been shown to have significant side effects, including respiratory suppression in children, so they are not recommended in young patients. Many practitioners do not prescribe them in patients younger than 12 years of age.[10-15] Prostaglandin analogs are typically not first-line for treatment of ocular hypertension associated with hyphema because of the possibility that they may increase intraocular inflammation.

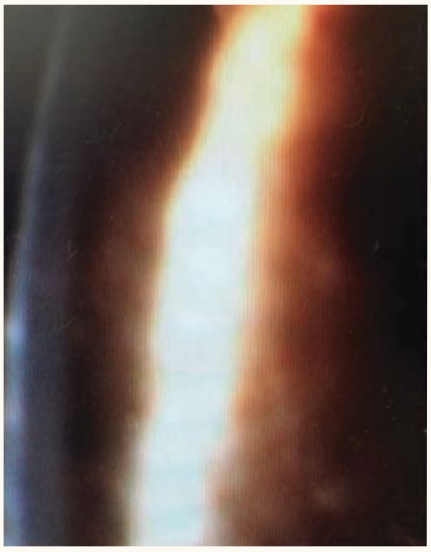
Periorbital and Orbital Cellulitis

Both of these conditions are also more common in children compared with adults.[16] Typical causes of periorbital and orbital cellulitis include chalazion/hordeolum, trauma and sinusitis. Orbital cellulitis is a more severe condition and requires imaging, hospitalization and IV antibiotics. If an abscess is present, the patient may require surgical drainage for treatment. Orbital cellulitis has a high association with sinusitis.

Both conditions present with a red, painful, swollen eyelid. In periorbital cellulitis, vision is not affected, other ocular structures are normal and ocular motilities remain intact. Orbital cellulitis signs can include afferent pupillary defect, extraocular motility restrictions, decreased vision and retinal and optic nerve findings as well as anterior chamber reaction. Any of these signs indicate an emergency hospitalization and further evaluation. Fever is not a good differentiator between orbital and periorbital cellulitis.

In cases of periorbital cellulitis, children under two years old—or someone unable to be compliant with oral medications—may require hospitalization. If a patient is on oral medications and still worsening, additional work-up is indicated. Typical follow-up after initiation of oral medications is two days. Strict return instructions with signs of worsening infection and orbital cellulitis should be given to the family. Worsening is an indication for potential hospital admission or emergency room services.[17]

Oral antibiotics to consider as first-line treatments include amoxicillin/clavulanate, cephalexin and clindamycin.[17-19] When dealing with a high prevalence of MRSA or an at-risk population, clindamycin should be considered as initial treatment. Worsening while on antibiotics or no improvement at 48 hours is a sign of inadequate treatment. Some sources advocate for clindamycin as a primary treatment instead of amoxicillin/clavulanate or cephalosporins due to increased incidence of MRSA.[20,21] Children over 40kg are typically given an adult dosage. Amoxicillin/clavulanate, cephalexin and clindamycin are available in oral suspensions. Consider probiotics or yogurt to prevent gastrointestinal upset while on oral antibiotics. In children under five years old and when prescribing



This case of active BKC and corneal infiltrates is best treated with combined topical antibiotics and steroids.

clindamycin, consider consulting the patient's pediatrician.[17]

Pediatric Lid Disease

This is another common issue among children. Blepharitis and chalazion can typically be conservatively managed with lid hygiene and warm compresses. If they do not resolve, referral for surgical removal may be suggested. Tetracyclines are contraindicated in younger children due to teeth discoloration and should not be used.

Occasionally after chalazion or trauma, a pyogenic granuloma can develop. These typically improve with a short course of topical steroids dosed two to three times daily. If large pyogenic granulomas do not improve with topical treatment, some surgeons will remove them. Others prefer to monitor because they typically do resolve over time.

Cases of blepharokeratoconjunctivitis (BKC) can cause irregular astigmatism, corneal scarring and be an amblyogenic factor in children. In its active phase, it is most often managed with topical steroids and antibiotics to reduce inflammation and bacterial load, as well as lid hygiene and warm compresses. Most treatments of BKC are off-label.

Hordeolum can also typically be treated in combination with lid hygiene and a topical antibiotic or topical antibiotic/steroid combination. An ointment is preferred. If topical medications are not improving the hordeolum and periorbital cellulitis is suspected, then an oral antibiotic should be considered.

Herpes Simplex Virus (HSV) Infections

Primary HSV-1 infections occur most commonly on the lips, but children can present with HSV dermatitis of the eyelids and HSV keratitis. Both topical ganciclovir and oral acyclovir have been studied and found to work well for treatment of herpes simplex keratitis.[22] Oral acyclovir is less expensive and is more readily covered by insurance, so it is a first-line choice for both pediatric herpes simplex keratitis and herpes simplex dermatitis of the eyelids. This is off-label use. Topical ganciclovir initial dosage is five times a day which could cause less compliance than oral medications. Topical ganciclovir has not been studied in children under two years old.[23] Avaclyr (acyclovir ophthalmic ointment 3%, Fera) was FDA-approved in 2019, but it is not commercially available, and its anticipated availability is currently unknown.

Recommended dosage of oral acyclovir in pediatrics changes frequently, so it is recommended to consult a prescriber's digital reference or the patient's pediatrician when prescribing oral antiviral medications in children. Because initial outbreaks of HSV infections are more likely to present with symptomatic infections, pediatricians frequently prescribe oral antiviral medications and are an excellent resource for dose recommendations. With oral valacyclovir, there is an increased cost, so more pediatric studies have looked at oral acyclovir for herpes simplex keratitis than valacyclovir. It can be dosed with less frequency, which is beneficial in pediatric patients.

Limbal infiltrates and injection in a patient with active BKC.

If the patient is having recurrent keratitis or dermatitis suppression, therapy may be indicated. A pediatrician or infectious disease expert should be consulted due to the increased risk of side effects with chronic suppression in children with oral antivirals due to renal effects.

Given HSV keratitis can be visually devastating in childhood, close follow-up and treatment is required. A higher percentage of children than adults may present with bilateral disease. Children in an amblyogenic age range may develop amblyopia as this is often a unilateral or asymmetric disease. This can be caused by transient opacification of the cornea during a critical period, corneal scarring or irregular astigmatism. In cases of irregular astigmatism, unilateral fitting of a rigid gas permeable or scleral lens may be required to optimize vision and treat amblyopia.[24-27]

Any time visual acuity is decreased in a child with a history of HSV keratitis, a trial period of amblyopia treatment is indicated. If best-corrected visual acuity after treatment is 20/40 or worse, the parents should be educated on the importance of polycar-

Table 1. Commonly Prescribed Combination Antibiotic/Steroid Meds[41-51]

Brand Name	Generic/Active Ingredient	Pediatric Use
Maxitrol and generic	neomycin/polymyxin B sulfates and dexamethasone (gtt and ung)	two years of age for gtt not established in ointment
Zylet	loteprednol etabonate 0.5% and tobramycin 0.3%	safety and effectiveness in pediatric patients have not been established
Tobradex and generic	tobramycin and dexamethasone (gtt and ung)	two years of age
Blephamide	sulfacetamide sodium 10% and prednisolone acetate 0.2% (gtt only, ung discontinued)	under six years of age has not been established
Pred-G	gentamicin sulfate and prednisolone acetate (gtt and ung)	safety and effectiveness in pediatric patients have not been established

bonate glasses for safety, especially if the child plays sports. Referral to a corneal specialist is warranted in recurrent disease and central corneal ulcers. Neonatal HSV and eczema herpeticum require emergent care. Eczema herpeticum is a disseminated rash occurring with HSV, associated with atopy and almost exclusively occurs in children.[24-27]

Allergic Conjunctivitis, Vernal (VKC) and Atopic Keratoconjunctivitis (AKC)

Allergies with ocular symptoms are another key pathology that can require optometric intervention.

Allergic conjunctivitis. Allergies are commonly present in childhood, and a high percentage of these children will have ocular symptoms. Allergic conjunctivitis can present seasonally or be year-round. The mainstay treatment is ophthalmic antihistamine and allergen avoidance. Cold compresses and artificial tears can also be used for comfort and to rinse the ocular surface of allergens.[28] Once daily antihistamine drops can be beneficial in children because they are easy to use and can increase compliance. If symptoms are not improving, a short course of topical steroids can be considered.[29]

VKC. This is a more serious form of ocular allergies in children that typically presents around eight years of age. It occurs more commonly in males and has a seasonal component, where it is usually worse in the spring and summer and improves in the winter. Hallmark signs are Horner Trantas dots, giant papillary conjunctivitis (GPC) or a combination of the two. Always look underneath the upper eyelid in suspected cases because sometimes GPC may be the only presenting sign. Horner Trantas dots also present more commonly in the upper limbal area of the cornea.

These patients are usually highly symptomatic, and topical antihistamines alone will not treat active disease. Topical steroids in conjunction with topical antihistamines are a first-line treatment with a goal of tapering off the topical steroid as symptoms improve.[30] If the patient's symptoms increase on tapering of topical steroids, or if they develop steroid-induced hypertension, topical cyclosporine or compounded tacrolimus can be considered.

There have been multiple studies showing the benefits of off-label use of topical immunomodulators such as topical cyclosporine or compounded tacrolimus for controlling inflammation and reducing recurrence of symptoms with VKC. Cyclosporine (Restasis, Allergan; Cequa, Sun Pharmaceuticals) at twice daily dosing in combination with a topical antihistamine is a good first option.[30] A generic version of cyclosporine will soon be available. Verkazia (Santen) is a new formulation of cyclosporine that was recently FDA-approved for treatment of VKC and will likely be available in the spring of 2022. It represents the first immunomodulator to be approved for treatment of VKC. Its safety and effectiveness have been studied in children four to 18 years of age. The recommended dosage is four times daily. Compounded tacrolimus 0.1% has also shown good efficacy in the treatment of VKC.[31-33]

AKC. This condition has findings very similar to VKC except that it does not have seasonal variation; AKC patients have signs and symptoms all year long. They also tend to have a history of atopy and symptoms presenting at an older age range, typically as teenagers. These patients are more likely to need immunomodulators to control disease and can have significant corneal changes that can affect vision. A corneal specialist referral may be indicated. All patients with AKC or VKC should be referred to an allergist if they have not already established care.

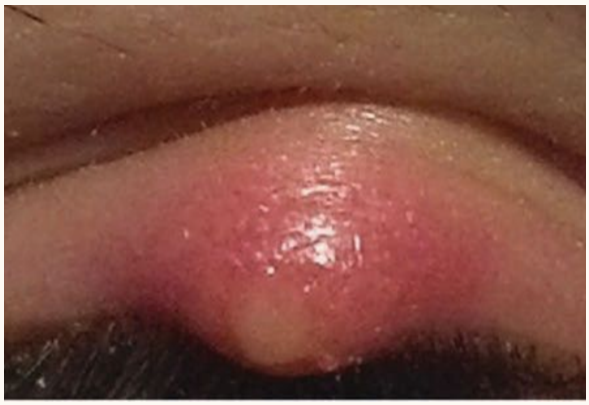
Topical Ophthalmic Medications

There are very few topical medications that are contraindicated in children, but not all have received approval for use in all ages of children. Most topical antibiotics and antihistamines have labeling for pediatric use. Most topical steroids do not have information in their labeling for pediatric use. Fluorometholone is approved for children two years and older.[34,35] The dosage of topical ophthalmic medications in children is typically the same as the adult dosage.

Exercise caution when keeping medications away from children, especially eye drops that usually do not have any type of child safety mechanism. In 2012, the FDA released information regarding over-the-counter eye drops and nasal sprays

Table 2. Commonly Prescribed Ophthalmic Antibiotics[4,41,52-59]

Brand Name	Generic/Active Ingredient	Pediatric Use
Azasite	azythromycin	one year of age
Besivance	besifloxacin	one year of age
Ciloxan	ciprofloxacin (gtt and ung)	two years of age
Gentasol/Gentak	gentamicin (gtt and ung)	safety in neonates not established
Erythromycin	erythromycin	all ages
Ocuflox	ofloxacin	one year of age
Vigamox	moxifloxacin	all ages
Zymar	gatifloxacin	one year of age
Zymaxid	gatifloxacin	one year of age
Levofloxacin	levofloxacin	one year of age



Hordeolum that would benefit from a topical antibiotic/ steroid combination ointment as first-line treatment.

with accidental ingestion in children. It is important to discuss drug safety with the family as a general course of practice. It is best to avoid any drugs containing tetrahydrozoline, naphazoline or oxymetazoline because there are other, more effective medications that can treat the same conditions.[36]

Since most ocular lubricants are not prescription-based, the FDA has not evaluated their use or safety in adults or children. These medications are commonly used in pediatric practice and generally considered safe for children.

Oral Medications

As a child grows, there are changes in absorption, metabolism, distribution and excretion of medications. This is one of the reasons why medications are based on weight, sometimes in conjunction with the age of the child. Typically, there is a maximum dose that is recommended, and the dose given should never exceed the adult dosage of the medication that is being prescribed. When treating children younger than five years old, it may be beneficial to contact the child's pediatrician when dosing medications.

The dosage recommendation for oral medications in children is based on mg/kg. The drug recommendations may be written as mg/kg/dose or mg/kg/day. It is important to differentiate this when referencing dosage recommendations. Dosage recommendations in children tend to change more frequently than adults, so it is important to always reference dosage recommendations prior to prescribing. Often if children are over 40kg and 12 years or older, the recommendation is the adult dosage, but it is important to always check as every medication is different.

Common Oral Antibiotics

There are several oral antibiotics ODs should be aware of when managing pediatric ocular pathology.

Augmentin. This is an excellent antibiotic for soft tissue infections, but the dosing can be somewhat challenging, and it does not provide MRSA coverage. It comes in multiple dose forms, and some are approved for only certain age or weight ranges. Some dose forms are divided into twice daily dosing, some into three times a day dosing. If the incorrect dose form is used, it can result in either too much or not enough clavulanate, which could cause undertreatment of the infection or significant gastrointestinal upset.[17]

Dosage is based on the amount of amoxicillin. Most recommended formulation for children with soft tissue infections is the 7:1 dose form. One commonly used 7:1 dose form of oral suspension is amoxicillin 400mg/clavulanate 57mg per 5ml.

Table 3. Commonly Prescribed Ophthalmic Steroids[34,35,41,60-66]

Brand Name	Generic/Active Ingredient	Pediatric Use
Alrex	loteprednol etabonate 0.2%	safety and effectiveness in pediatric patients have not been established
FML	fluorometholone alcohol 0.1%	two years of age
FML ointment	fluorometholone alcohol 0.1%	two years of age
Lotemax SM	loteprednol etabonate 0.38%	safety and effectiveness in pediatric patients have not been established
Lotemax gel	loteprednol etabonate 0.5%	safety and effectiveness in pediatric patients have not been established
Lotemax ointment	loteprednol etabonate 0.5%	safety and effectiveness in pediatric patients have not been established
Pred Mild	prednisolone acetate 0.12%	safety and effectiveness in pediatric patients have been established, use in pediatric patients is supported by evidence from adequate and well-controlled studies of prednisolone acetate ophthalmic suspension in adults with additional data in pediatric patients
Pred Forte	prednisolone acetate 1%	safety and effectiveness in pediatric patients have been established, use in pediatric patients is supported by evidence from adequate and well-controlled studies of prednisolone acetate ophthalmic suspension in adults with additional data in pediatric patients
Durezol	difluprednate 0.05%	Durezol was evaluated in a three-month, multicenter, double-masked trial in 79 pediatric patients (39 Durezol, 40 prednisolone acetate) zero to three years of age for the treatment of inflammation following cataract surgery that found a similar safety profile between both groups

The most common recommended dosage is between 25mg/kg/day and 45mg/kg/day in divided twice daily dosage form, not to exceed 1,750mg of amoxicillin a day.[33] For children with periorbital cellulitis, pursuing the higher end of the dose range may help reduce the risk of undertreating the infection. Some sites suggest not prescribing ES-600 suspension in patients 40kg and over due to lack of data on ES-600 suspension in this patient category.[37]

Keflex. This medication is also a treatment option for periorbital cellulitis. The recommended dosage for Keflex is 25mg/kg/day to 100mg/kg/day divided into doses every six to eight hours, not to exceed 2,000mg/kg/day. For children over 40kg and adults, the recommended dosage is one gram twice a day.[38] It does not provide MRSA coverage.

Clindamycin. This treatment can be considered as a first-line or when MRSA is suspected. It is contraindicated in infants and has more side effects than Augmentin and Keflex. Consult a pediatrician for dosage due to the increased risk of side effects. It has been associated with severe colitis.

Bactrim. There is a higher rate of allergies with Bactrim due to sulfa-containing medication, but it can be considered in suspected MRSA infections. Consult a pediatrician prior to prescribing due to the increased risk of side effects. It should not be used as a monotherapy due to poor coverage of *Streptococcus*.[20]

Antiviral Medications

Topical ganciclovir is approved for treatment of HSV keratitis in children aged two and older. Oral acyclovir has been studied and works well as an off-label treatment for HSV keratitis in children.[22,23] Oral acyclovir is less expensive and is more readily covered by insurance, so it is our first-line choice for both herpes simplex keratitis and herpes simplex dermatitis of the eyelids. Recommended dosage of oral acyclovir in pediatrics changes frequently, therefore I would always recommend consulting a prescriber's digital reference or the patient's pediatrician when prescribing acyclovir.

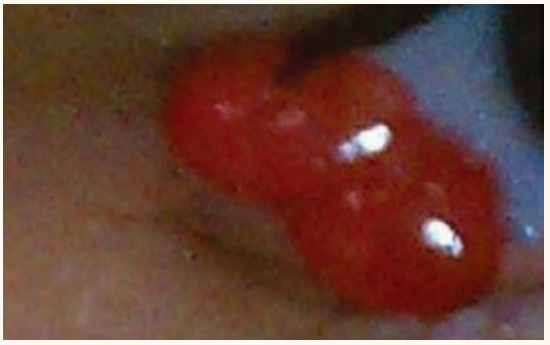
Contraindicated Medications

Just as an optometrist must know which drug options to choose, it is equally important to recognize when a medication is contraindicated for a patient.

Alpha agonists. These medications are typically contraindicated in children younger than eight to 12 years old due to the significant side effect profile. This would also be a contraindication for the use of apraclonidine in suspected Horner's syndrome in young children. Brimonidine and apraclonidine HCl are not recommended for use due to central nervous system effects and respiratory suppression in young children.[11-15]

Apraclonidine may have a safer side effect profile than brimonidine, but there have been case reports of central nervous system effects in young infants on apraclonidine, especially those who are younger than six months of age.[39] No approved antidote is currently available for use in alpha-2 agonist toxicity, but some poison control centers may recommend naloxone. If a patient had known exposure to these medications and is exhibiting extreme drowsiness, inability to rouse or other signs of respiratory suppression, they should go to the emergency department immediately.[11-15]

Tetracyclines. This treatment is relatively contraindicated in children younger than eight years old due to the risk of tooth discoloration. The minimum age used to be 12 years old but has been decreased to eight years old due to completion of tooth calcification by this age. In most ophthalmic infections, there are other medications with a better safety profile in children.[40]



A pyogenic granuloma that occurred post-chalazion. First-line treatment is topical steroids. They are often hidden under the lid, and Chi will evert when the lid is pulled down.

Takeaways

In summary, there are many anterior segment conditions that present uniquely or more commonly in children that can be treated with topical and oral medications. Most topical ophthalmic medications are dosed the same as adult dosages. If children require oral medications, they should always be dosed by weight in mg/kg. It is often beneficial to consult a prescriber's digital reference or the patient's pediatrician because dosage of medications in children change more often than adults.

More medications are being researched in pediatrics, and most topical ophthalmic medications have been approved for use in children. It is always important to make sure that there are no significant contraindications prior to prescribing for children. A comprehensive understanding of the available options and how to use them is key when caring for this patient population. ■

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OPTOMETRIC STUDY CENTER QUIZ

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1. Which common cause of bacterial conjunctivitis has been associated with otitis media?
a. *Staphylococcus*.
b. *Streptococcus*.
c. *Haemophilus influenza*.
d. None of the above.

2. Which is not a differentiating sign in periorbital vs. orbital cellulitis?
a. Proptosis.
b. Reduced vision.
c. Diplopia.
d. Fever.

3. Which condition does not typically have seasonal increases in symptoms?
a. Allergic conjunctivitis.
b. AKC.
c. VKC.
d. None of the above.

4. Which is the treatment of choice for periorbital cellulitis where MRSA is not suspected?
a. Amoxicillin/clavulanate.
b. Doxycycline.
c. Cephalexin.
d. Both a and c.

5. Which steroid is approved for children aged two and older?
a. Prednisolone acetate 1%.
b. Fluorometholone.
c. Loteprednol etabonate.
d. Prednisolone acetate 0.12%.

6. Which are differentials for a recurrent red eye in children?
a. BKC.
b. HSV keratitis.
c. Uveitis.
d. All of the above.

7. A two-year-old comes in with a small corneal abrasion. Which would be the first-line treatment?
a. Pressure patch.
b. Bandage contact lens.
c. Prednisolone acetate.
d. Erythromycin ointment.

8. Which is the amoxicillin/clavulanate formulation recommended for soft tissue infections?
a. 7:1.
b. 13:1.
c. 6:1.
d. 12:1

9. The dosage recommendations of amoxicillin/clavulanate are based on the amount of which ingredient?
a. Amoxicillin.
b. Clavulanic acid.
c. Cephalexin.
d. Both a and b.

10. The calculated dosages of oral medications should never exceed which?
a. The amount a child can swallow.
b. The maximum daily dose.
c. The recommended adult dose of the medication.
d. Both b and c.

11. There is a rapid in-office test for conjunctivitis available for which of the following pathogens?
a. *Staphylococcus*.
b. *Haemophilus influenza*.
c. Adenoviral virus.
d. None of the above.

12. Which is the first-line treatment for VKC?
a. Topical steroids.
b. Topical antibiotics.
c. Topical antihistamines.
d. A combination of topical steroids and topical antihistamines.

13. In cases of recurrent VKC or steroid-induced hypertension, which other medications can be considered for off-label use?
a. Cyclosporine.
b. Prednisolone acetate.
c. Compounded tacrolimus.
d. Either a or c.

14. At which weight and age is the adult dosage of a medication often recommended for children?
a. Over 35kg; 10 years or older.
b. Over 40 kg; 10 years or older.
c. Over 40kg; 12 years or older.
d. The adult dosage of a drug is never recommended for children.

15. The most common cause of orbital cellulitis is which?
a. Hordeolum.
b. Trauma.
c. Sinusitis.
d. None of the above.

16. The preferred treatment for HSV keratitis in children is which?
a. Oral acyclovir.
b. Topical acyclovir.
c. Topical ganciclovir.
d. Trifluridine.

17. Which of the following conditions represents a medical emergency and requires hospitalization with IV antibiotics?
a. Periorbital cellulitis.
b. Eczema herpeticum.
c. Orbital cellulitis.
d. Chalazion.

18. Which condition occurs almost exclusively in children, typically accompanied by atopy, and represents a medical emergency?
a. Eczema herpeticum.
b. Orbital cellulitis.
c. VKC.
d. None of the above.

19. Which class of glaucoma medications is contraindicated in young children?
a. Prostaglandins.
b. Beta blockers.
c. Alpha agonists.
d. None of the above.

20. Why should oral tetracycline medications not be given in children younger than eight years old?
a. Taste.
b. Stomach upset.
c. Risk of papilledema.
d. Tooth discoloration.

Examination Answer Sheet

Managing Pediatric Ocular Pathology

Valid for credit through March 15, 2025

Online: This exam can be taken online at revieweducationgroup.com. Upon passing the exam, you can view your results immediately and download a real-time CE certificate. You can also view your test history at any time from the website.

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Answers to CE exam:

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives. *1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent*

21. Appraise how to treat pediatric ocular pathologies. ① ② ③ ④ ⑤
22. Identify which drugs are approved for what ages. ① ② ③ ④ ⑤
23. Select the right medication and dosage for various conditions. ① ② ③ ④ ⑤
24. Describe strategies to minimize adverse effects when treating pediatric patients. ① ② ③ ④ ⑤

25. Based upon your participation in this activity, do you intend to change your practice behavior? (Choose only one of the following options.)

Ⓐ I do plan to implement changes in my practice based on the information presented.

Ⓑ My current practice has been reinforced by the information presented.

Ⓒ I need more information before I will change my practice.

26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

27. If you plan to change your practice behavior, what type of changes do you plan to implement? (Check all that apply.)

Ⓐ Apply latest guidelines
Ⓑ Change in diagnostic methods
Ⓒ Choice of management approach
Ⓓ Change in current practice for referral
Ⓔ Change in vision correction offerings
Ⓕ Change in differential diagnosis
Ⓖ More active monitoring and counseling
Ⓗ Other, please specify: _____

28. How confident are you that you will be able to make your intended changes?

Ⓐ Very confident Ⓑ Somewhat confident Ⓒ Unsure Ⓓ Not confident

29. Which of the following do you anticipate will be the primary barrier to implementing these changes?

Ⓐ Formulary restrictions
Ⓑ Time constraints
Ⓒ System constraints
Ⓓ Insurance/financial issues
Ⓔ Lack of interprofessional team support
Ⓕ Treatment related adverse events
Ⓖ Patient adherence/compliance
Ⓗ Other, please specify: _____

30. Additional comments on this course: _____

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31. The content was evidence-based. ① ② ③ ④ ⑤
32. The content was balanced and free of bias. ① ② ③ ④ ⑤
33. The presentation was clear and effective. ① ② ③ ④ ⑤

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

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OVERVIEW

The East Coast Optometric Glaucoma Symposium (ECOGS) meeting will be held as a hybrid event. ECOGS will be simulcast virtually for remote participants to provide a flexible and accessible educational experience. This 2-day biannual symposium is designed to provide optometrists with exposure to current thinking on evolving standards of care, state-of-the-art technology and breaking research that will guide current and future glaucoma care in the optometric setting. Incorporating cases, clinical pearls, and discussion sessions, the program will maximize the opportunity for participant/faculty engagement.

The OGS conferences are long-running and trusted programs for optometrists managing patients with glaucoma. Each East Coast symposium focuses on glaucoma diagnosis and management, with the West Coast symposium focusing on therapies and innovations for comprehensive glaucoma coverage.

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Water, Sclerals Don't Mix

Exposure increases the chances of microbial infection.

Q Many gas permeable (GP) lens wearers rinse their lenses with water. There seems to be a consensus that scleral lens exposure to water carries an even greater risk. Is this true? If so, what makes this modality different than small-diameter GP lenses?

A "Both GP and soft lenses can act as vectors for microbes, ultimately resulting in ocular infections," according to Mile Brujic, OD, of Ohio, David Kading, OD, of Washington and Nikhita Jacobs, an incoming optometry student. Lenses exposed to water are of significant concern, especially due to the presence of *Acanthamoeba*.[1-3] This organism exists in both cystic and trophozoite forms and, as such, is extremely resistant and exists within water.[3]

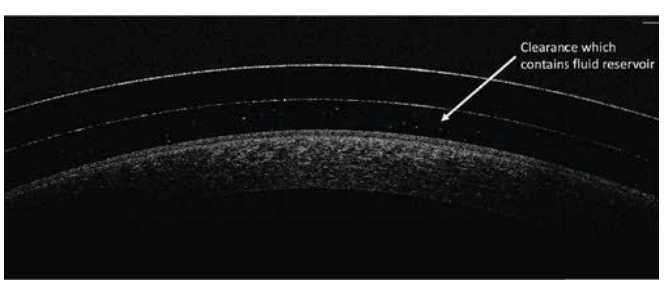
Best Care Practices

GP contact lens wearers have a bad habit of rinsing their lenses in water, note Drs. Brujic and Kading and Ms. Jacobs. Lens rinsing can occur prior to storage in multipurpose disinfecting solution, after removal from the solution in preparation for lens application to the eye or after manual lens cleaning.[4] Some patients even go as far as storing their lenses in water. Drs. Brujic and Kading have seen all of these scenarios in their practices.

Contact lenses should never come in contact with water, Drs. Brujic and Kading and Ms. Jacobs emphasize. The trio adds that contamination of lenses with *Acanthamoeba* specifically can cause sight-threatening infections and should be avoided at all costs. They highlight patient education as a possible solution to breaking bad habits. Also, observing patients apply and remove their lenses may help pinpoint shortcomings in the lens care process.

If swimming in contact lenses, Drs. Brujic and Kading and Ms. Jacobs recommend wearing goggles that effectively minimize exposure to water. If showering in lenses, direct contact with water should be avoided.

Scleral lenses present an additional challenge, they caution. Small-diameter GPs move with every blink, increasing the chances that microbes will be removed from the lens surface. On the other hand, scleral lenses, when fit appropriately, should maintain very little movement on the surface of the eye. Consequently, the fluid reservoir that is present between the cornea and the posterior surface of the lens will remain in contact with the cornea throughout the day. As such, appropriate care of this lens modality is critical to optimize corneal safety. Any contact between water and scleral lenses exposes the cornea to unnecessary and avoidable risk.[5]



The space between the posterior lens surface and the anterior corneal surface contains the fluid reservoir.

Scleral lenses are often fit using diagnostic fitting sets, Drs. Brujic and Kading and Ms. Jacobs note. Accordingly, it is critical to understand and follow contemporary scleral lens disinfecting protocols to ensure they are appropriately and properly disinfected. Several organizations, including the American Optometric Association, American Academy of Optometry, Gas Permeable Lens Institute and Contact Lens Manufacturers Association, collaborated to create a consensus on in-office disinfection protocols.[6] After any scleral lens is placed on a patient's eye, it should go in a 3% hydrogen peroxide non-neutralizing case for three hours. The lens should then be rinsed with multipurpose solution, patted and stored dry. It shouldn't be exposed to water at any point during this process.

Additionally, contemporary hydrophilic surface treatments, such as Tangible Science's Hydra-PEG, provide a more comfortable wearing experience. They also minimize surface deposits, as lens exposure to water can remove the surface treatment. ■

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About Dr. Shovlin

Dr. Shovlin, a senior optometrist at Northeastern Eye Institute in Scranton, PA, is a fellow and past president of the American Academy of Optometry and a clinical editor of *Review of Optometry* and *Review of Cornea & Contact Lenses*. He consults for Kala, Aerie, AbbVie, Novartis, Hubble and Bausch + Lomb and is on the medical advisory panel for Lentechs.

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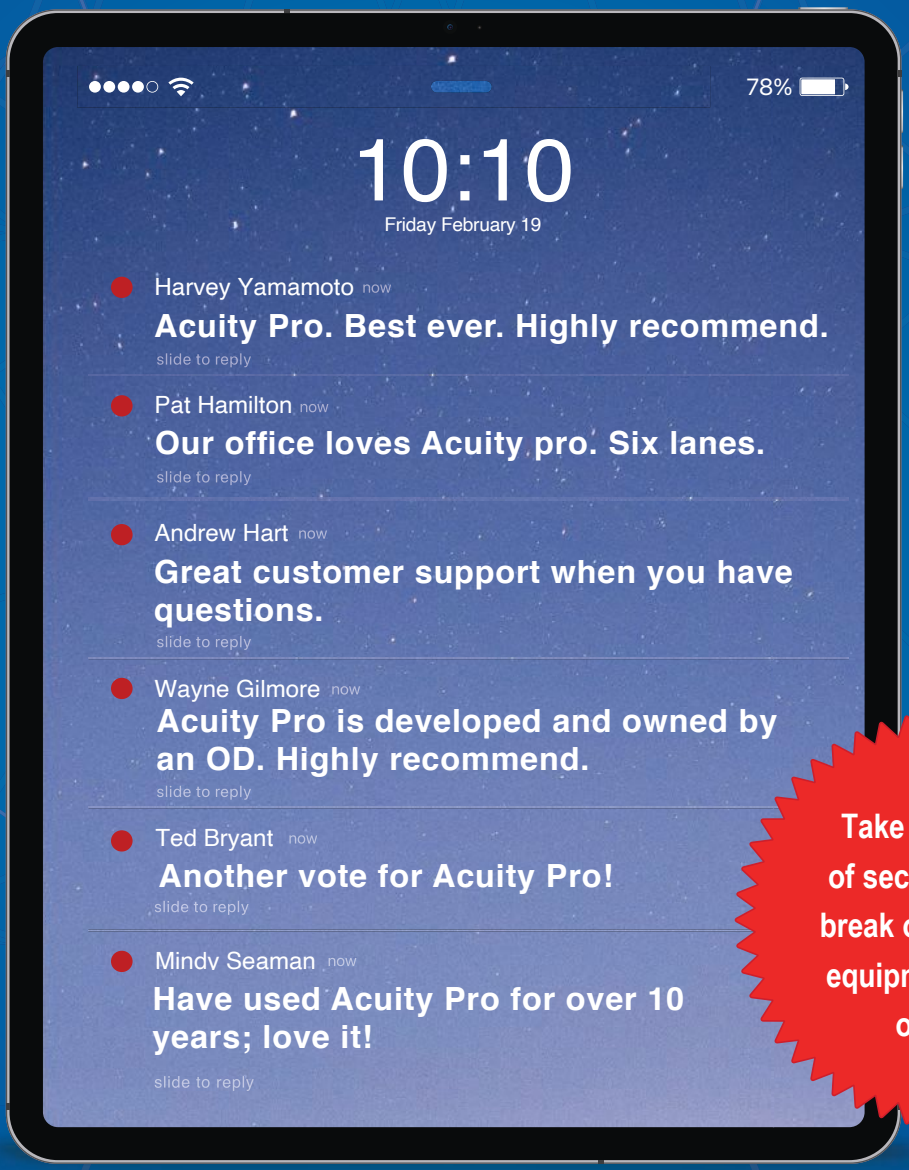

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BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

A Sticky Subject

Mucin dysfunction in dry eye is more common than you think.

Refinement of our conception of tear film structure has taken us from seeing mucins as a stand-alone layer to an integral part of the mucoaqueous matrix.[1] Mucins contribute very little to the thickness of the tear film, but their role is much greater than their share of ocular real estate implies. Mucins are vital to ocular surface protection and stability.[2,3]

Consider this: without mucins, the tear film could not readily adhere to the eye.[2,3] As such, it's no wonder that mucin-deficient dry eye can be so insidious. However, this seemingly rare form of dry eye disease (DED) may be more frequent than we assume. In fact, mucin dysfunction is now said to be common in all forms of moderate to severe DED, which has prompted interest in more thoughtful diagnosis and inspired new research on treatment aimed at fortifying this important structure.[4]

Mucins Explained

Understanding what stimulates mucin secretions and how to regulate it is an area rich in research potential. Mucins are produced throughout the body, but ocular surface mucins in particular are generated by goblet cells—apical cells of the conjunctiva and cornea and the lacrimal gland.[4] Meibomian gland secretions also contribute to the mucin content found on the tear film.[1] Mucins are high-molecular weight glycoproteins that contribute to the mucus layer, promoting cell adhesion and defending against ocular surface damage.[2,3,5]

Mucus, on the other hand, is a lubricant that prevents desiccation of the ocular surface during blinking by dissipating energy.[1] Mucus gel also traps bacteria and irritants so that they can be removed during blinking.[1] Furthermore, mucins help stabilize the tear film and help maintain hydration.[6]

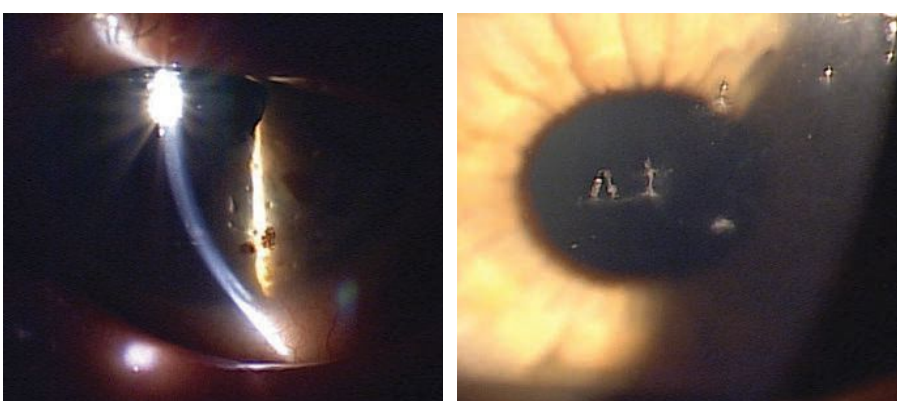
Some mucins are membrane-bound to epithelial cells, while others are secreted diffusely throughout the tear layers.[4] MUC5AC and MUC2 are secreted mucins whereas MUC1, MUC4 and MUC16 are membrane-bound.[4] Importantly, both forms contribute to ocular surface health in different ways.[4] For example, MUC5AC is a gel-forming mucin that traps allergens and pathogens.[7] MUC2 and MUC5AC are gel-forming mucins that affect how much water can be retained in the tear film.[1]

Diagnosing Dysfunction

It is well-established that dry eye can occur in response to decreased mucin levels. Goblet cell loss is a common feature of every form of DED.[8] Relatedly, when goblet cell density decreases, MUC5AC production also decreases and disease severity increases.[8] Although some studies have shown the expression of the MUC5AC gene doesn't change depending on DED status, MUC5AC levels appear in lower concentrations in the tears of patients with DED.[9] Interestingly, evidence suggests that mucin deficiency is both a cause and a consequence of DED.[4] Specifically, goblet cell loss is related to inflammation *subsequent* to hyperosmolarity, yet mucus deficiency also has been shown to *sustain* hyperosmolarity and inflammation.[10]

Although there is no conclusive marker for mucin-deficient dry eye, several tests can help us tease out the extent to which mucins are responsible for each patient's unique presentation. These include ocular surface staining, particularly conjunctival staining, fluorescein corneal staining for mucin plaques and filaments, impression cytology, laser scanning confocal microscopy and tear film instability measurements.[4]

Specifically, the use of rose bengal can demonstrate reduced goblet cell density and epithelial cell mucin expression. However, due to discomfort and phototoxicity, rose bengal is not used as frequently as the nontoxic vital dye lissamine green, which can detect dead and degenerated cells.[4]



Filamentary keratitis with mucin and epithelial cells adhering to the corneal surface.

About Dr. Karpecki

Dr. Karpecki is medical director for Keplr Vision and the Dry Eye Institutes of Kentucky and Indiana. He is the Chief Clinical Editor for *Review of Optometry* and chair of the New Technologies & Treatments conferences. A fixture in optometric clinical education, he consults for a wide array of ophthalmic clients, including ones discussed in this article. Dr. Karpecki's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

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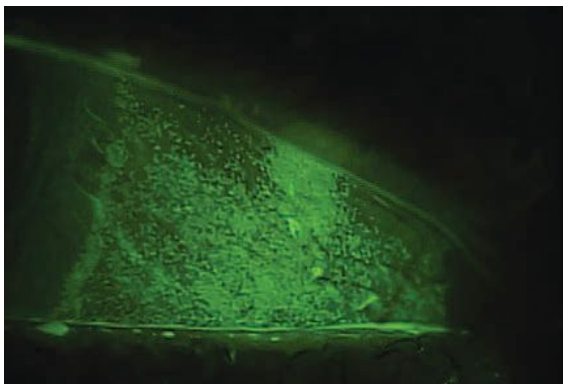

Staining of the conjunctiva in a mucin-deficient dry eye.

For ocular staining assessments that extend beyond the conjunctiva, fluorescein sodium is most suitable, as it allows for corneal examination.[4] Note that staining both structures is preferred to obtain a comprehensive clinical picture. For instance, without conjunctival staining, mucus fishing syndrome would be difficult to diagnose. Although dyes can be used to assess tear film instability, interferometry and topography allow for quantifiable non-invasive measurement.

Keep in mind that inflammation and mucin expression are closely linked. In fact, inflammatory mediators act directly on goblet cells, modulating proliferation, differentiation, apoptosis and function.[4] Furthermore, neurogenic inflammation is connected to mucin dysfunction, owing to the fact that goblet cell secretion is stimulated via a reflex arc from the afferent sensory nerves in the cornea to the efferent sympathetic and/or parasympathetic nerves of the conjunctiva.[4] Importantly, nerve growth factor can stimulate mucin secretion and has been shown in animal studies to increase goblet cell numbers.[11,12]

Other inflammatory diseases associated with mucin dysfunction include filamentary keratitis, superior limbic keratoconjunctivitis and mucus fishing syndrome.

Treating Dysfunction

Several agents have been proposed as potential treatments to restore mucin function.[4] For example, viscoelastic gel lubricant drops containing hyaluronic acid, carbomers and HP-guar are said to be "mucin-like" in function.[4] In addition, recombinant human lubricin was shown to reduce signs and symptoms in patients with moderate dry eye.[13]

Three mucin secretagogues (diquafosol tetrasodium, rebamipide and vitamin A) are also potential treatments.[4] Diquafosol tetrasodium facilitates mucin production and tear secretion and is currently approved as an ophthalmic solution at 3% concentration outside the United States.[4] The quinolone derivative rebamipide is also under investigation due to its anti-inflammatory and antioxidant properties.[4]

Both oral and topical vitamin A have been investigated as treatments.[14] Vitamin A ointment for DED recently became available in the US as Optase Hylo Night and is a practical and important option doctors can use and implement right away. Using vitamin A supplementation is also logical, considering that deficiency is linked to goblet cell loss.[4]

In terms of anti-inflammatories, studies of approved agents frequently address issues relating to goblet cell function as well as clinical signs consistent with mucin deficiency or expression. As discussed above, nerve growth factor is also an area of current investigation.

In addition to treatments aimed at restoring function, mucolytics can decrease mucus discharge.[4] Specifically, topical 5% N-acetylcysteine (NAC) has mucolytic, anti-inflammatory and antioxidant properties, and regulates mucus secretion while reducing mucus accumulation in the conjunctival sac in dry eye patients.[4] Studies demonstrate that NAC reduces symptoms these patients, as well as improves signs and symptoms in MGD patients and improves TBUT and mucus ferning patterns in blepharitis patients.[15-18] Oral mucolytics may also be considered, although these may further disturb the tear film.[4]

On Closer Inspection

Changes in mucins are not only present in advanced disease; rather, this can be the very first signal that a patient has ocular surface disease.[4] Furthermore, although historically mucin deficiency was thought to be a rare cause of DED, renewed attention highlights the need for more careful examination during the diagnostic process.[4] With newer treatments demonstrating targeted effects, the imperative to conduct more thorough investigations is pronounced.[4]

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BY ALISON BOZUNG, OD

URGENT CARE

Variations on a Theme

Two patients presented with vitreous hemorrhages but under very different circumstances.

A 35-year-old Hispanic female presented to the ophthalmic emergency department with vision loss OD for one week. Visual acuities were 20/70 OD and 20/50 OS. Intraocular pressures, pupils and anterior segment findings were normal. The right fundus had preretinal and vitreous hemorrhages (VHs) centrally, intraretinal hemorrhages and neovascularization along the major arcades (*Figure 1*). The left had hemorrhages and intraretinal microvascular abnormalities without neovascularization. OCT was also employed (*Figure 2*).

The patient's medical history was significant for type 1 diabetes. She reported uncontrolled blood glucose levels consistently measuring above 300mg/dL. She was diagnosed with a VH secondary to proliferative diabetic retinopathy (PDR) in the right eye.

Another patient, a 67-year-old Hispanic male, presented with blurred vision OD for five days accompanied by dark spots and "spider webs." Visual acuities were 20/100 OD and 20/20 OS. There was no neovascularization anteriorly, but a diffuse VH was seen in the right eye. The left eye fundus exam was unremarkable. Due to the limited view of the right fundus, an ultrasound was conducted, revealing a posterior vitreous detachment (PVD) without a retinal break or detachment (*Figure 3*).

The patient was advised to sleep with his head elevated and discontinue any non-prescribed blood thinners. Frequent observation with repeat ultrasonography was suggested. At last follow-up, the patient's vision had improved to 20/25, and no retinal neovascularization or break was visible. He was diagnosed with a hemorrhagic PVD and did not require further intervention.

Etiology

These two patients have the same diagnosis, but their conditions are very different. VH can present for a multitude of reasons. Determining the best treatment underscores the importance of first reaching the correct diagnosis. Though exceptions exist, there are four main factors to consider when faced with a VH:

1. The most common etiology of a VH is neovascularization, and PDR remains the number one cause of all VHs.[1] Intraocular neovascularization from ischemia can arise from numerous systemic conditions including diabetes, sickle cell anemia and leukemia.[2,3] Ophthalmic conditions such as retinal vein or artery occlusions, ocular ischemic syndrome, chronic uveitis and chronic retinal detachment can also lead to neovascularization and VH.

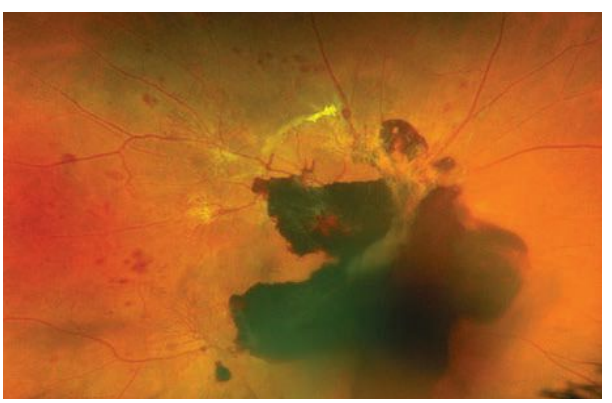

Fig. 1. Fundus photo of the first patient shows vitreous and subhyaloid hemorrhages with active neovascular fronds extending from the arcades.

2. The second cause of VHs is the rupture of a normal blood vessel. This can occur spontaneously or after ophthalmic trauma and is often seen in retinal tears, detachments and PVDs in part due to the strong vitreoretinal adhesions over retinal vessels.[4] It is important to remember that eyes with a VH in the setting of an acute PVD have a 54% to 91% chance of a retinal break.[5] Vessels on the optic nerve head are also susceptible to leakage when there is a shearing force or severe disc edema. More rarely, patients with Valsalva retinopathy or Terson's syndrome may experience a hemorrhage that breaks into the vitreous cavity.

3. Third, consider the potential for an abnormal retinal vascular formation to rupture. Retinal arterial macroaneurysm lesions may lead to a VH.[6,7] Clinical evidence of a lesion of this nature includes an extensive or multi-layered hemorrhage with or without a possible breakthrough VH. Rarer vascular causes of a VH are prepapillary loops and congenital retinal macrovessels.[8,9]

4. Finally, the choroid may be implicated in a VH. The retinal pigment epithelium (RPE) typically serves as a barrier between the choroidal circulation and the retina, but in cases of RPE breakdown, there remains potential for further complications. VHs have also been well-documented in conditions such as exudative age-related macular degeneration, choroidal melanoma and polypoidal choroidal vasculopathy.[10-12]

About Dr. Bozung **Dr. Bozung** works in the Ophthalmic Emergency Department of the Bascom Palmer Eye Institute (BPEI) in Miami and serves as the clinical site director of the Optometric Student Externship Program as well as the associate director of the Optometric Residence Program at BPEI. She has no financial interests to disclose.

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Evaluation

When a patient with a VH presents, a review of systems should be completed. Knowledge of diabetes or a blood dyscrasia such as leukemia should raise suspicion of vascular compromise from ischemia. In cases where a systemic disease process is suspected, evaluation of the fellow eye is a crucial step.

In our first patient, the fellow eye examination supported diabetic retinopathy as a likely etiology. It is also beneficial to know the prior status of the affected eye. Inquire if the patient has had any previous ocular trauma, ophthalmic diagnoses, ocular surgeries, retinal laser procedures or intravitreal injections. A patient who was treated with intravitreal anti-VEGF agents for a retinal vein occlusion, for example, could be at an increased risk of intraocular neovascularization. Finally, symptoms such as photopsia or web-like floaters prior to vision loss could suggest an underlying PVD, retinal tear or retinal detachment.

Dynamic ultrasonography remains the gold standard for visualization of the vitreous cavity and retina in the case of a VH. In cases of ocular trauma, however, an open globe should first be ruled out given the risk of further globe compromise when pressure is applied. VHs often appear as mobile, poorly defined, low-level echoes.[13] Attention should be directed to the retinal surface to evaluate for vitreoretinal traction, breaks or detachments. Additionally, ensure there are no choroidal masses present. Overall, diagnoses can be reliably made by those with experience in obtaining and reviewing imaging, but small retinal breaks can still be missed on ultrasonography, even by an experienced ultrasonographer or physician.[14,15]

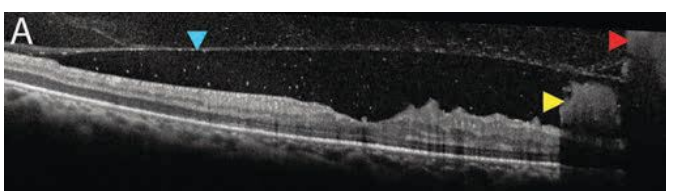

Fig. 2a. OCT raster scan of the foveal pit demonstrates posterior hyaloid face (blue arrow) with both subhyaloid and preretinal hemorrhages (yellow arrow) and a VH (red arrow).

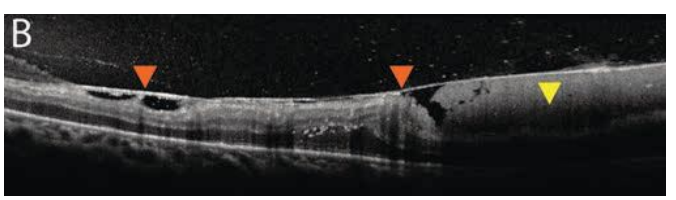

Fig. 2b. An additional OCT image shows a thickened hyaloid with an adherent or "sticky" retina (orange arrows). The subhyaloid hemorrhage can be seen here in higher quality (yellow arrow).

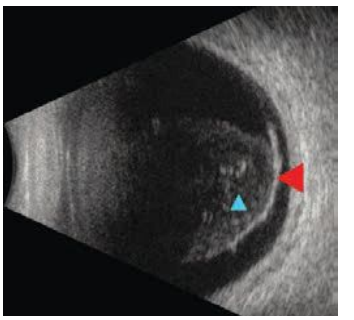

Fig. 3. Ultrasound reveals a detachment of the posterior hyaloid face from the retina (red arrow). Notable vitreous debris (blue arrow) was appreciable on clinical exam as a hemorrhage.

Management

In general, the treatment of VHs is variable and dependent on the underlying condition. In cases of a VH from PDR, neither panretinal photocoagulation (PRP) nor intravitreal injection alone has been shown to improve the clearance rate of the hemorrhage, but PRP in isolation or in combination with anti-VEGF injections can prevent future VH episodes.[16] Patients with neovascularization from PDR or retinal vein occlusions typically receive PRP to the ischemic retina once the VH clears enough to allow for visualization. If a retinal tear or detachment is visualized on ultrasonography, the patient should be referred to a retina surgeon emergently. Though there are proponents of early vitrectomy for a fundus-obscuring VH of any etiology, a decision may also be made to carefully monitor a patient with a VH as long as there is no ultrasonographic evidence of a retinal tear or etiology, as in the case of our second patient.[5,17]

A VH typically takes one to six months to clear, though they tend to resolve quicker in eyes that have undergone vitrectomy or syneresis. Non-clearing VHs are defined as those lasting longer than three months, and this is often an indication for vitrectomy regardless of etiology.

In all cases, a careful and systematic approach to evaluating VHs remains paramount. Referral and management strategy depends on the underlying pathology, so remain aware of the main etiologies behind this condition. ■

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Seeing Red

A trip to the emergency department is necessary to treat this condition.

BY RAMI ABOUMOURAD, OD
MIAMI

A 68-year-old Caucasian male presented with acute vision loss for eight days. He described a sudden and painless decline in right eye visual acuity that had remained stable since onset. He denied associated flashes, floaters, light sensitivity, recent trauma or any symptoms in the other eye. His past medical history included hypertension, which was controlled with lisinopril, metoprolol and furosemide. He had no known drug allergies and noted an unremarkable eye exam one month prior.

Upon examination, his uncorrected visual acuity was counting fingers at four feet OD with no pinhole improvement and 20/70 OS with pinhole improvement to 20/30. The pupils were equally round, but there was a marked relative afferent pupillary defect (rAPD) in the right eye. Confrontation visual field testing revealed a central scotoma with peripheral constriction in the right eye, but was normal in the left eye; extraocular motilities were full. Intraocular pressure (IOP) was 12 mm Hg OD and 13 mm Hg OS. The patient was pseudophakic OU and had an otherwise unremarkable anterior segment exam. Dilated fundus exam of the left eye was completely normal. The right eye, however, showed findings, as seen in *Figures 1 and 2*.

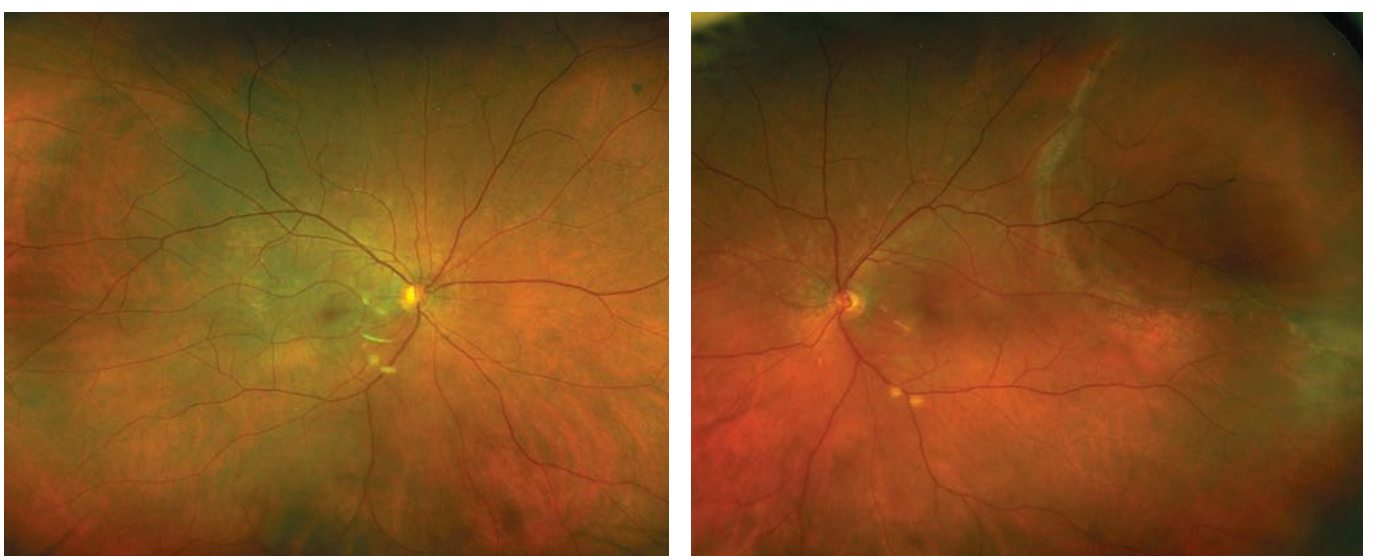
Take the Retina Quiz

1. Which of the following best describes the OCT of the right eye?
a. Central inner-segment/outer-segment loss.
b. Inner retinal thickening and hyperreflectivity.
c. Inner retinal thickening and intraretinal fluid.
d. Outer retinal thinning/atrophy.

2. What is the diagnosis for the patient's vision loss in the right eye?
a. Branch retinal artery occlusion.
b. Carotid retinal artery occlusion.
c. Central retinal artery occlusion.
d. Ophthalmic artery occlusion.

3. What would be the most appropriate next step in the management of this patient?
a. Intravitreal bevacizumab in the right eye.
b. Observation.
c. Pars plana vitrectomy in the left eye.
d. Transfer to emergency room.

4. What is the most likely visual prognosis of this patient's right eye?
a. 20/40 or better.
b. Counting fingers.
c. Full recovery back to baseline.
d. No light perception.



Figs. 1 and 2. Ultra-widefield fundus photography of the right eye (left) and left eye (right).

About Dr. Dunbar **Dr. Dunbar** is the director of optometric services and optometry residency supervisor at the Bascom Palmer Eye Institute at the University of Miami. He is a founding member of the Optometric Glaucoma Society and the Optometric Retina Society. Dr. Dunbar is a consultant for Carl Zeiss Meditec, Allergan, Regeneron and Genentech.

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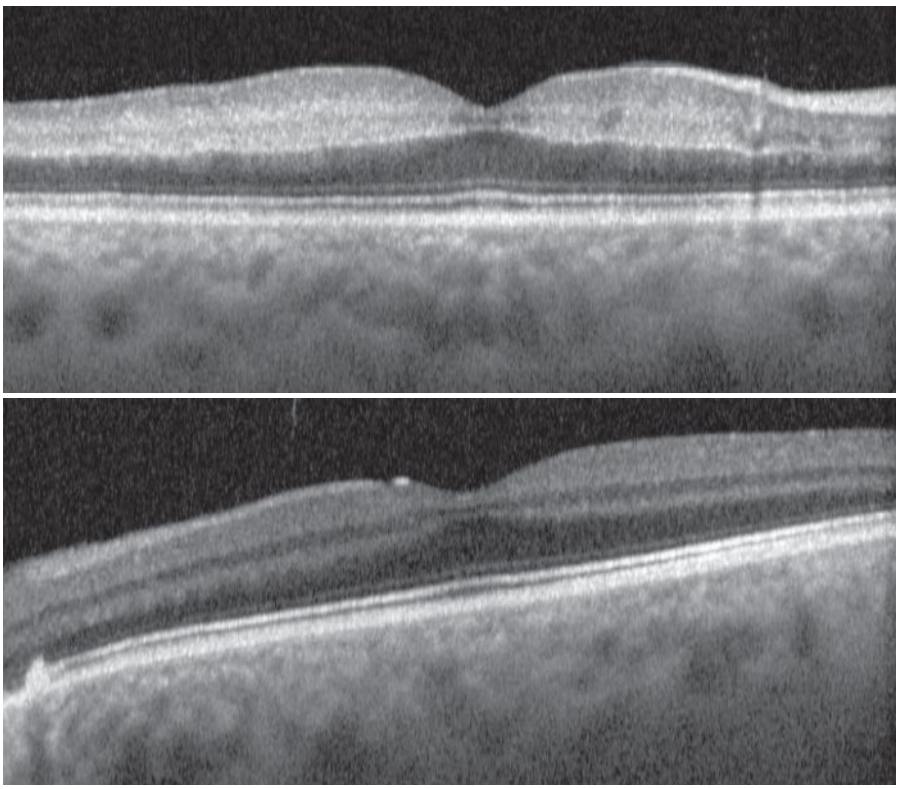

Figs. 3 and 4. OCT of the right eye (top) and left eye (bottom).

5. Which of the following is not considered conservative standard treatment?

a. Anterior chamber paracentesis.
b. Intra-arterial tissue plasminogen activator.
c. Ocular hypotensive eye drops.
d. Ocular massage.

For answers, see page 114.

Diagnosis

The fundus exam of the right eye revealed mild retinal whitening of the posterior pole with a subtle cherry-red spot, suggestive of a central retinal artery occlusion (CRAO). Of interest, he also had a superotemporal macula-on retinal detachment with a complete pigment demarcation line in the left eye, suggesting chronicity; this was an incidental finding and completely unrelated to his vision loss (*Figure 2*).

OCT of the right macula showed diffuse inner retinal thickening and hyper-reflectivity without intraretinal or subretinal fluid, consistent with a CRAO. The left eye was normal.

Given the diagnosis of a CRAO, we initiated an emergent transfer to the emergency department for an immediate systemic work-up. Imaging of the brain, head, neck, heart and serology testing for giant cell arteritis (GCA), was negative. However, urinary toxicology screening revealed the presence of cocaine metabolites. The cardiology team felt that the most likely etiology of CRAO in this patient was vasospasm in the setting of cocaine use.

Discussion

While the true incidence of CRAO is not known, it is estimated to comprise about one out of 10,000 cases at tertiary care referral centers.[1,2] There is a male predilection and it is more common in older adults with an average age of 60; over 90% of cases are in patients over the age of 40.[1,2] The disease largely presents unilaterally with potential for sequential eye involvement, but rarely presents simultaneously and bilaterally in 1-2% of cases.[1,2]

The pathophysiology of arterial obstructions is primarily via one or a combination of the following five mechanisms: embolism, vascular narrowing, thrombosis, arterial spasm and reduction in blood flow caused by carotid or ophthalmic artery obstruction, systemic hypotension or elevated intracranial pressure.[3]

Typically, patients retain at least light perception vision; thus, in cases of no light perception, choroidal circulation has likely been compromised due to carotid or ophthalmic artery obstruction.[3] Rubeosis iridis at presentation should raise suspicion for concomitant carotid artery obstruction.[1]

Clinically, the site of arterial obstruction is only visible in 20% to 25% of cases, suggesting that thrombotic events are more frequently the etiology of CRAOs compared to embolic events.[2] Other causes of CRAO include vasculitis (*i.e.* GCA), optic neuritis and local trauma.[2]

On clinical exam, the earliest signs are diffuse retinal whitening of the posterior pole with a central cherry-red spot, as mentioned earlier. Retinal whitening indicates acute retinal ischemia and represents opacification of the retinal nerve fiber (RNFL) and ganglion cell layer (GCL).[3] The foveola is perfused by the underlying choriocapillaris, so this normal tissue appears cherry-red in contrast to the surrounding hypoxic tissue; normal retinal transparency typically returns two to three weeks after onset.[1,3]

Peripheral retina typically appears grossly normal due to thinner RNFL and GCL.[1,3] Other possible vascular signs include arteriolar narrowing, boxcarring or segmentation; arteriolar emboli may also be visible on clinical exam.[3] Typically, a marked rAPD can be observed within seconds of onset.[3]

The natural disease course results in optic atrophy, inner retinal atrophy, retinal arterial attenuation and cilioretinal collaterals.[1] About 20% of patients may develop neovascularization (anterior segment more commonly than posterior segment) typically four weeks after onset.[1,5]

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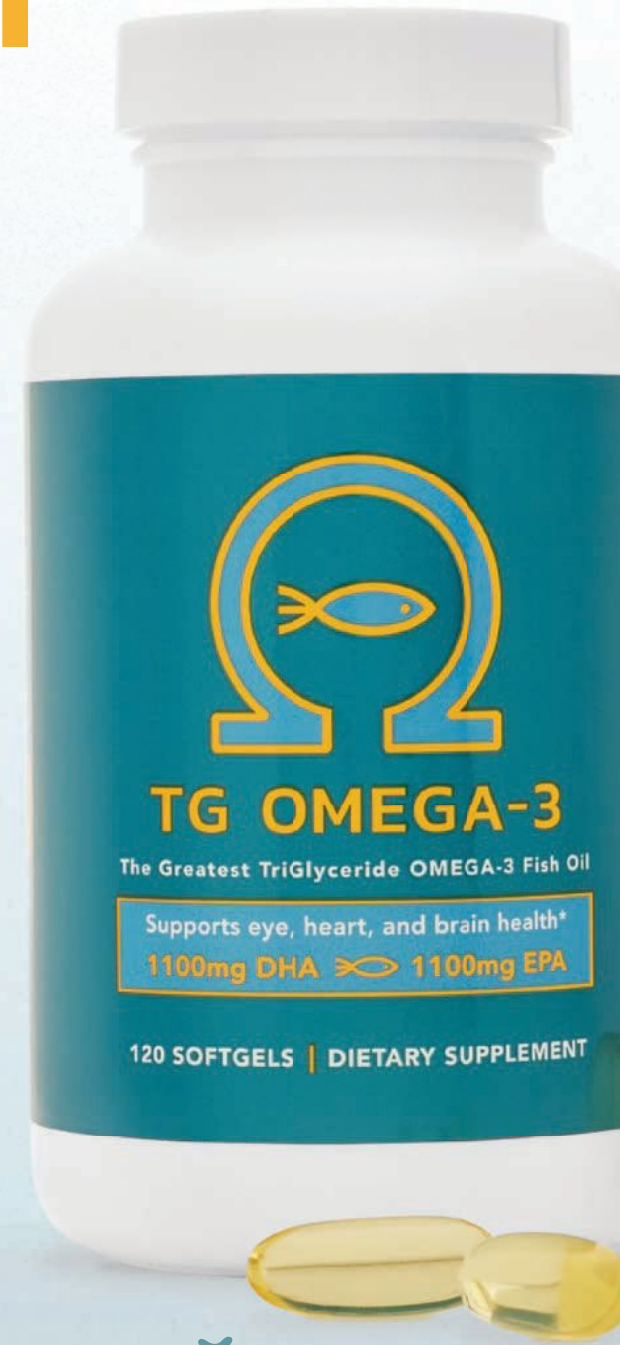

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Treatment

The vision loss from CRAO is severe and irreversible with no proven effective treatment options. Due to the rapidity of tissue damage, attempted intervention may only be indicated if patients present within a few hours of onset. The optimal window has been reported to be within the first 100 minutes, but some clinicians feel that there is still indication to treat within the first four to six hours. Unfortunately, most patients tend to present an average of one week after symptom onset.[1,6]

CRAOs are true ophthalmic emergencies and require immediate transfer to the nearest hospital for complete stroke work-up and neurology/cardiology consultation to rule out underlying, impending or concomitant disease (*i.e.* GCA or cerebrovascular accident).[1,5,6] Patients with CRAO are at greatest risk for systemic morbidity within the first seven days after symptom onset, which makes their often delayed presentation problematic.[6]

If primary etiologies for CRAO are uncovered during systemic evaluation, they should be treated appropriately in efforts to spare the fellow eye. Otherwise, conservative standard treatment aims to aid retinal reperfusion through procedural or pharmacologic means. Options include ocular massage (digital or contact gonioscopy lens compression) or rapidly decreasing IOP with topical and/or systemic meds, or with anterior chamber paracentesis.[5, 6]

In general, these patients require long-term follow-up to monitor for neovascularization in the affected eye, as well as to ensure optimal ocular health in the fellow eye. Monocular precautions should be discussed (protective eyewear/polycarbonate lenses) and a low vision referral is warranted.

Our patient returned one week later for evaluation. He was counseled on the guarded prognosis of the right eye and the need to monitor for complications such as neovascularization. The decision was made to closely monitor him at this time given the asymptomatic nature and signs of chronicity. ■

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ABOUT THE AUTHOR

Dr. Aboumourad currently practices at Bascom Palmer Eye Institute in Miami. He has no financial disclosures.

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▶ CORRECTIVE LENSES

Allergy-Fighting Contact Lens Now FDA-Approved

Most soft contact lenses aim to be minimally disruptive to the ocular surface to keep from altering the delicate balance of forces that maintain the tear film, but a new entrant launched in early March takes an active role for the first time by releasing an antihistamine to fight allergy. The lens, Acuvue Theravision (Johnson & Johnson), contains 19mcg of the antihistamine ketotifen. It's the first of several drug-eluting contact lenses expected in the coming years.

Allergic conjunctivitis patients can get relief as quickly as three minutes after insertion, J&J says. The effect can last up to 12 hours, according to the company, but the lens may be worn for longer for vision correction. It's important not to use the lens on an eye that's already red or if redness develops during wear, a press release notes. The company also explicitly states that care products are not to be used.

Theravision is made of the familiar etafilcon A material common to the Acuvue product line and is intended for daily disposal. It's available in powers of -12D to +6D. There is no toric component, so patients need to have no more than 1D of astigmatism.

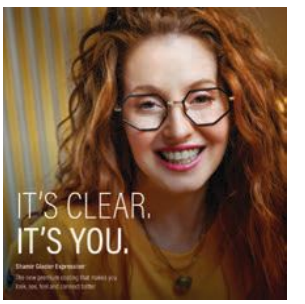
J&J says that 40% of contact lens wearers suffer from itchy eyes due to ocular allergies, nearly 80% of those with ocular allergy find the experience frustrating and 50% consider eye drops inconvenient and would prefer an alternative option.

Filter Combats Light Sensitivity

Conditions such as frequent migraines or traumatic brain injury sometimes lead patients to experience light sensitivity, which can compromise vision quality and aggravate symptoms. Filtered lenses, such as one just released by Eschenbach, are one effective treatment consideration for patients with this complaint. The new lens option, called Acunis FL-41, aims to improve sensitivity by reducing transmission of the light wavelengths responsible for glare, the company said in a press release.

Based on their visual needs, the Acunis FL-41 filter is offered in three tints: light (25% absorption), medium (50% absorption) and dark (75% absorption). Each can accompany one of four different frame selections, two made of stainless steel and two made of acetate.

AR Coating Improves Contrast Sensitivity, Aesthetics



A common complaint from spectacle wearers—and whoever may be talking to them—is the distracting reflections caused by light rays "bouncing off" the lenses of their glasses. Thankfully, lens manufacturers have long used antireflective coatings to reduce reflections and improve overall visual quality. One such company, Shamir Optical, recently launched a new AR coating called Glacier Expression that it touts as something even better than existing products.

According to Shamir, people wearing glasses coated with Glacier Expression demonstrated a 25% increase in contrast sensitivity vs. standard AR coating (no brand was specified), leading to improved reaction times during daily activities such as night driving. The company says the new coating also improves how wearers look to others—thereby improving person-to-person connection—and how their eyes feel, by reducing eye strain.

Shamir also recently announced an update to its Autograph Intelligence PAL that the company says better reflects real-world visual needs, particularly during computer use.

▶ DRY EYE

Disposable Device Aids Nighttime Lid Closure

Lagophthalmos patients now have a new way to improve nighttime eyelid closure. Announced last fall and now shipping, SleepTite/SleepRite is a see-through shield to be worn over the eyelids at night. It keeps lids sealed shut to prevent ocular exposure to fluids, airborne contaminants and excessive drying, to reduce DED and MGD symptoms, says start-up company Ophthalmic Resources Partners. Options are available for both regular and sensitive skin types in boxes of 30 pairs, a press release explains.

The disposable devices feature a non-irritating adhesive designed to stay in place all night and not pull on lashes or skin, and a tab on the outer edge also makes for easy removal in the morning, the release explains. Though the devices are made to be put over the eyelids each night, patients who wish to alternate every other night will still see clinical improvement, the company says. ■

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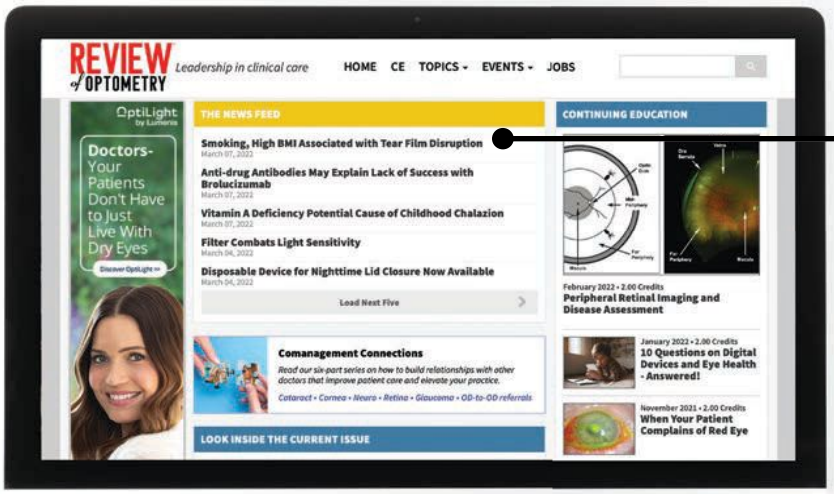

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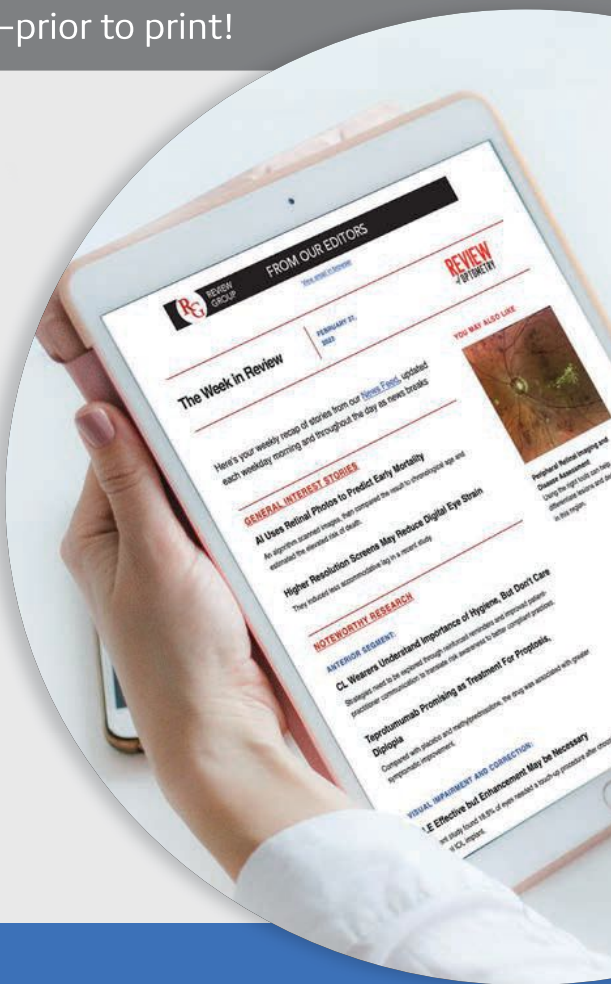

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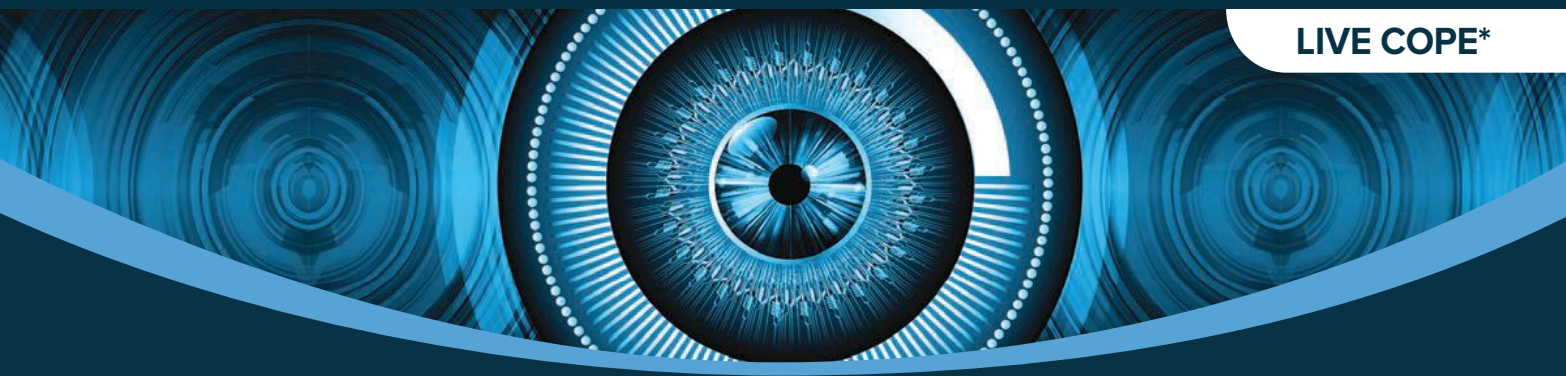

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BY ANDREW S. GURWOOD, OD

DIAGNOSTIC QUIZ

Medication Mishap

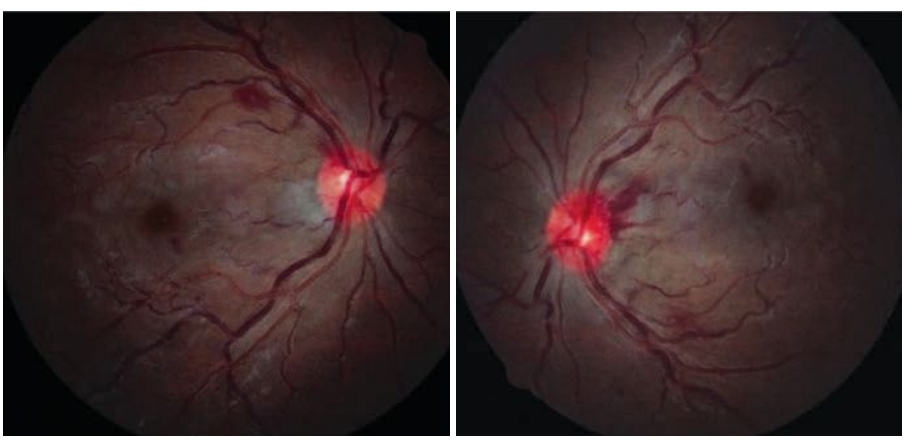
A complex case goes awry after beginning a new therapy. Can you sort out what happened and how to document it?

A 74-year-old African-American male presented with a chief complaint of redness and pain in both eyes of two days' duration. His ocular history was remarkable for bilateral cataract extraction, which had been performed two years prior.

His systemic history included diabetes, hypertension, hypercholesterolemia and a recent diagnosis of multiple myeloma, for which he was started on a new medication. His systemic medications included glipizide, Humalog (insulin lispro), lisinopril, metoprolol, simvastatin, prochlorperazine maleate, Velcade (bortezomib), dexamethasone and Zometa (zoledronic acid).

Clinical Findings

His best-corrected visual acuities were 20/20 OD and OS at distance and near. All external testing was unremarkable and there was no afferent defect. Slit lamp exam revealed Grade 1+ conjunctival injection OU and Grade 2+ cells with trace flare and ciliary flush OU. Intraocular pressures were measured at 9mm Hg OD and 10mm Hg OS by Goldmann applanation. The significant dilated fundus findings are demonstrated in the photographs.



Fundus evaluation revealed these findings. What do these images suggest about his status? What laboratory results might you expect based on this presentation?

Additional laboratory work up is indicated for both the anterior segment and retinal findings, especially in the present of his considerable medication regimen. The recommended blood panel would include:

- complete blood count with differential and platelets (CBC c Diff and platelets)
- chest x-ray (CXR)
- human leukocyte antigen test (HLA B27)
- reactive plasma reagin test (RPR)
- fluorescent-*Treponemal* antibody absorption study (FTA abs)
- angiotensin-converting enzyme study (ACE)
- rheumatoid factor (RF)
- lipid profile
- fasting blood sugar (FBS) level
- human immunodeficiency virus assay (HIV titre)
- assay of clotting factors (prothrombin time, activated partial thromboplastin time)

Blood sugar and glycosylated hemoglobin should also be measured.

Your Diagnosis

What would be your diagnosis in this case? What is the patient's likely prognosis? To find out, please read the online version of this article at www.reviewofoptometry.com. ■

About Dr. Gurwood Dr. Gurwood is a professor of clinical sciences at The Eye Institute of the Pennsylvania College of Optometry at Salus University. He is a co-chief of Primary Care Suite 3. He is attending medical staff in the department of ophthalmology at Albert Einstein Medical Center, Philadelphia. He has no financial interests to disclose.

Retina Quiz Answers (from page 104)—Q1: b, Q2: b, Q3: d, Q4: b, Q5: b

NEXT MONTH IN THE MAG

In April, we present our annual cornea report. Articles will include:

- Foreign Body Removal: A Step-by-Step Guide for ODs
- Managing Keratoconus with CXL: What's New, What's Next?
- Test Your Corneal Disease Diagnosis Skills
- Herpes Simplex Keratitis Management Do's and Don'ts

Also in this issue:

- Pediatric Series: Spectacles vs. Surgery for Binocular Vision Management
- How to Add Low Vision Interventions to Your Practice

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1. CVI data on file 2021. Prospective, subject-masked, randomized, bilateral, two-week cross-over dispensing study at 5 US sites with MyDay® multifocal and DAILIES TOTAL1® Multifocal; n=58 habitual multifocal contact lens wearers.
2. CVI data on file 2020. Prospective, double-masked, bilateral, one-week dispensing study UK with MyDay® multifocal; n=104 habitual multifocal contact lens wearers.

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