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Leadership in clinical care

14th Annual Pharmaceuticals Report

- Systemic meds
- Antibiotics
- Mydriatics and miotics
- Glaucoma care

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STAY ALERT FOR SYSTEMIC MED SURPRISES

Many ocular adverse effects may be hiding inside your patient's pill bottle. Here's a new way to think about them.

Page 34

ALSO INSIDE

UPLIFTED

INDICATION

Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Alpha-adrenergic agonists as a class may impact blood pressure. Advise Upneeq patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens.
- Use Upneeq with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
- Upneeq may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop.
- Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

RVL PHARMACEUTICALS, INC.

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PM-US-UPN-0197 01/21

Give Ptosis Patients an EYE-OPENING Lift With a Daily Drop of Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%[1]

The only FDA-approved prescription eyedrop proven to lift upper eyelids in adults with acquired blepharoptosis (low-lying lids)[1]

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UPNEEQ®
(oxymetazoline hydrochloride ophthalmic solution), 0.1%*

*Each mL of Upneeq contains 1 mg of oxymetazoline hydrochloride, equivalent to 0.9 mg (0.09%) of oxymetazoline free base.

Eye-Opening Possibilities

ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with Upneeq were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

DRUG INTERACTIONS

- Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.
- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact RVL Pharmaceuticals at 1-877-482-3788. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see next page for Brief Summary of full Prescribing Information.

Reference: 1. Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%. [Prescribing Information].

Learn more at Upneeq.com

™

UPNEEQ® (oxymetazoline hydrochloride ophthalmic solution), 0.1%,* for topical ophthalmic use

*Each mL of UPNEEQ contains 1 mg of oxymetazoline hydrochloride, equivalent to 0.9 mg (0.09%) of oxymetazoline free base.

BRIEF SUMMARY: The following is a brief summary only; see full Prescribing Information at https://www.upneeq.com/Upneeq-PI.pdf for complete information.

1 INDICATIONS AND USAGE

UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults.

2 DOSAGE AND ADMINISTRATION

Contact lenses should be removed prior to instillation of UPNEEQ and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 15 minutes between applications.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. UPNEEQ should be used with caution in patients with severe or unstable cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

5.2 Potentiation of Vascular Insufficiency

UPNEEQ should be used with caution in patients with cerebral or coronary insufficiency, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

5.3 Risk of Angle Closure Glaucoma

UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

5.4 Risk of Contamination

Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

6 ADVERSE REACTIONS

6.1 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.

A total of 360 subjects with acquired blepharoptosis were treated with UPNEEQ once daily in each eye for at least 6 weeks in three controlled Phase 3 clinical trials, including 203 subjects treated with UPNEEQ for 6 weeks and 157 subjects treated with UPNEEQ for 12 weeks. Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.

7.2 Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. [see Data]. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogenesis (28 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogenesis (278 times the MRHOD, on a dose comparison basis). Maternal toxicity, including decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat prenatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (28 times the MRHOD, on a dose comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 mg/kg/day (14 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (7 times the MRHOD, on a dose comparison basis).

8.2 Lactation

Risk Summary

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UPNEEQ and any potential adverse effects on the breastfed child from UPNEEQ.

8.4 Pediatric Use

Safety and effectiveness of UPNEEQ have not been established in pediatric patients under 13 years of age.

8.5 Geriatric Use

Three hundred and fifteen subjects aged 65 years and older received treatment with UPNEEQ (n = 216) or vehicle (n = 99) in clinical trials. No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects.

10 OVERDOSAGE

Accidental oral ingestion of topical intended solutions (including ophthalmic solutions and nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep UPNEEQ out of reach of children.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

RVL PHARMACEUTICALS, INC.

Manufactured for: RVL Pharmaceuticals, Inc.
Bridgewater, New Jersey 08807

PM-US-UPN-0203 01/21

No Clinical Advantage to Femto Cataract Surgery

Study finds equal levels of vision, safety and patient-perceived quality vs. traditional methods.

Femtosecond laser–assisted cataract surgery (FLACS) has received much buzz since it was introduced over a decade ago, but there is uncertainty about whether this high-tech, high-price approach offers any clinical benefits over conventional surgery using manual techniques. For this reason, researchers from London decided to study and report 12-month outcomes of a randomized controlled trial comparing FLACS with conventional methods.

Visual acuity, refraction, central corneal thickness, endothelial cell loss, adverse events, quality of life outcomes and patient-reported outcome measures (PROMs) were recorded for 400 patients (single eye surgery for each). There were no differences in corrected or uncorrected visual acuity, corneal thickness (compared to pre-op), endothelial cell loss (compared to pre-op and one month post-op), residual refractive cylinder, spherical equivalent refractive error from target refractions or changes in PROM indices. Mean uncorrected distance visual acuity was 0.12 logMAR for FLACS and 0.13 logMAR for conventional phaco. Rates of spherical equivalent refraction within 0.5D of target were 78% for FLACS and 81% for conventional phaco.

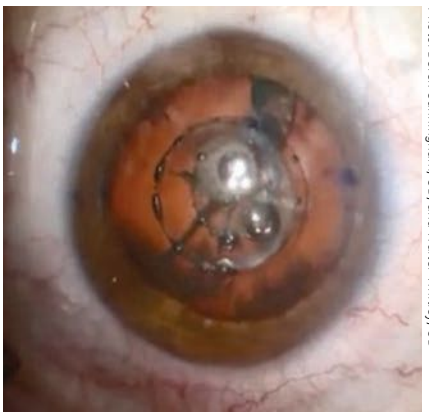

Photo: Derek Cunningham, OD, and Walter Whitley, OD

The authors concluded that FLACS was not superior to conventional phaco, as it did not provide any benefits in outcomes and it incurred higher costs.

The authors concluded that FLACS was not superior to conventional phaco, as it did not provide any benefits in outcomes and it incurred higher costs. A little more than half (58.5%) of the 400 patients attended a 12-month follow-up exam.

"Our results indicated that both groups had excellent visual and refractive outcomes at 12 months with no statistically significant difference in any of the tested parameters," the authors explained in their study. "Although validated cataract surgery-specific PROMs at one month postoperatively have been reported, this is the first time the same PROMs at 12 months postoperatively have become available" for a study of femto cataract vs. conventional approaches. "In contrast with other studies, we did not find that FLACS resulted in more predictable refractive outcomes."

Visual outcomes remain unchanged and, moreover, the femto approach wasn't any safer, they found. "The rate of onset of new visually significant comorbidities in the fellow eye between four weeks and 12 months was not significantly different between the FLACS group and the [conventional phaco] group."

Stanojcic N, Roberts HW, Wagh VK, et al. A randomised controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery: 12-month results. Br J Ophthalmol. 2021;105(5):631-8.

IN BRIEF

■ **Patients who underwent intravitreal therapy have an increased risk of intraoperative complications during cataract surgery**. A new model can predict the risk of complications such as posterior capsule rupture and zonular dehiscence. This large-scale study included 900,000 eyes from the Swedish National Cataract Register. **Overall, the rate of intra-op complications was 0.86%.** Patients were more likely to encounter complications if they had BCVA of 1logMAR or greater, were older than 90, male or diabetic or had pseudoexfoliation, glaucoma or previous intravitreal therapy. Other predictors included surgeon experience (fewer than 600 surgeries), use of rhexis hooks, blue staining and mechanical pupil dilation.

Af Segerstad PH. Risk model for intraoperative complication during cataract surgery based on data from 900,000 eyes: previous intravitreal injection is a risk factor. Br J Ophthalmol. April 22, 2021. [Epub ahead of print].

■ New research suggests **greater BMI may be linked with higher acute optic neuritis severity in males** with multiple sclerosis. The investigation also reports that the hormones estrogen and leptin appeared to influence the ocular condition in men with MS.

The study enrolled 61 MS patients whose acute optic neuritis severity and recovery (based on VA) was evaluated before, during and after the relapse. Males with moderate/severe acute optic neuritis had higher BMI (31.26 vs. 25.73), greater serum estrogen levels (32.24nmol/L vs. 23.06nmol/L) and enhanced serum leptin rates (12.29ng/mL vs. 4.1ng/mL) compared with male subjects with mild acute optic neuritis.

Of note: the researchers didn't observe these same findings in female patients.

Chu DT, Rosso M, Gonzalez CT, et al. Obesity is association with the optic neuritis severity in male patients with multiple sclerosis. Mult scler relat disord. March 21, 2021. [Epub ahead of print].

Smartphone Apps Fare Poorly at Vision Testing

Researchers identified three as the best of the bunch, yet stressed these too had limitations.

Visual acuity apps aren't in the ballpark of comparability to in-person refractions, but new research that analyzed 24 currently available platforms suggests three that seem to perform the best if an office visit isn't feasible, such as when offering remote screenings for telehealth consults.

"A growing number of ophthalmic health tool apps are available for both patients and clinicians, which may address the increasing demand for eye care in the future. As they are a relatively new form of technology, they are not without disadvantages," the research team from the UK wrote in their paper.

Compared with traditional VA testing that relies on printed optotypes, smartphone apps suffer from a range of variables that can influence the accuracy of results. This includes screen size, aspect ratio, pixel density, contrast and screen brightness, the study noted.

With these limitations in mind, here are the three apps the authors said would be suitable for clinical practice under appropriate circumstances:

Peek Acuity (Peek Vision)

The standalone app measures VA using the tumbling E test and includes an interactive guide on proper usage. The app begins by measuring VA monocularly at a 2m distance. The optotype decreases in size as the patient correctly identifies its direction until the final VA is reached. If the patient is unable to identify the direction of the optotype at 2m, the user is prompted to decrease the test distance to 1m. If the patient fails to identify the optotype at 1m, the user is instructed to decrease the test distance to 30cm.

The app offers two additional prompts corresponding to decrease VA, including a moving target, and ability to perceive the phone's torchlight. Final VA is expressed as logMAR (0.0), and this can be switched to Snellen metric (6/6) or Snellen imperial (20/20). Peek Acuity has been clinically validated and shown to produce accurate and repeatable acuity measurement compared with conventional acuity charts in peer-reviewed research, the researchers noted.

Photo: Bisant Labib, OD

Variables can impact smartphone apps' accuracy compared with printed optotypes.

Peek Acuity Pro (Peek Vision)

The Pro version of the app is a CE-registered, class 1, medical device available in certain countries, and both versions (Peek Acuity and Peek Acuity Pro) are available for free on the Google Store. The two apps have methods for calibrating both optotype size and brightness.

The limitation of these two apps is the inability for users to self-test, since the test requires a second person to act as the device operator. In the context of ophthalmic telehealth consults, this would limit the suitability of the app to patients living with friends or family members who can accurately operate the device, the authors noted.

Looc-Mobile Eye Test (Looc GmbH)

When testing near vision, the calibration stage of this app involves using a mirror and the phone's front facing camera to estimate the user's interpupillary distance, which takes around 30 seconds to complete. The app uses a phone's front-facing camera and face detection to determine the distance the device is being held from the face when measuring near VA, using the Landolt C or tumbling E optotype. The testing process involves the user identifying the direction of the optotype of increasing or decreasing size depending on the user response. This is a test of monocular VA, and acuity is presented as a Snellen imperial.

This novel technique of calibration has not been employed by any of the other apps tested; however, there are some inherent limitations, the investigators said. The method relies on detecting facial landmarking, which varies greatly depending on the optics of the camera being used, most notably the focal length. Additionally, the LooC–Mobile eye test hasn't been clinically validated. Still, the app has been created according to the International Organization for Standardization criteria for VA testing and has been implemented in individual ophthalmology clinics in Berlin with good results, the researchers said.

The team started by conducting a systemic search for VA testing apps on the Google Play and Apple App stores. They narrowed it down to 16 (67%) that tested near vision, five (21%) that measured distance and three (13%) that offered both. Out of the 24 apps, only five (21%) offered a method of calibration of optotype size, while the three previously mentioned (13%) demonstrated evidence of clinical validation.

More work is needed in vision testing smartphone applications, including the clinical validation of individual apps, improved governance of health apps and cohort management systems for the integration of these programs into existing care pathways, the study concluded.

Kawamoto K, Stanojcic N, Olivia JP, Thomas PBM. Visual acuity apps for rapid integration in teleconsultation services in all resource settings: a review. Asia Pac J Ophthalmol. February 9, 2021. [Epub ahead of print].

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References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Efron N, Jones L, Bron AJ, et al. *Invest Ophthalmol Vis Sci.* 2013;54(11):TFOS98-TFOS122. **3.** *Ocul Surf.* 2007;5(2):75-92.

Ocular Hypertension to POAG Conversion Rate Low, Study Finds

Optometrists have long known that ocular hypertension is a risk factor for development of primary open-angle glaucoma (POAG), but anticipating disease manifestation is a perennial problem for doctors monitoring such cases. In a recent study, researchers determined the cumulative incidence and severity of POAG after 20 years of follow-up among participants in the Ocular Hypertension Treatment Study (OHTS). The data from this long-term follow-up can be used to inform ocular hypertension management.

In phase one of the seminal study, participants were randomized to receive either topical ocular hypotensive therapy (medication group) or close observation (observation group). In phase two, both groups received medication. In phase three, participants received eye exams and visual function assessments.

Over 1,600 individuals were randomized in phase one of the trial. Of those, 483 participants (29.5%) developed POAG in one or both eyes (unadjusted incidence). After adjusting for exposure time, the 20-year cumulative incidence of POAG in one or both eyes was 45.6% among all participants, 49.3% among participants in the observation group and 41.9% among participants in the medication group. The 20-year cumulative incidence of POAG was 55.2% among African American participants and 42.7% among participants of other races, but the authors noted "when patients are stratified by baseline risk, Black/African American individuals and others in the same risk category have similar outcomes."

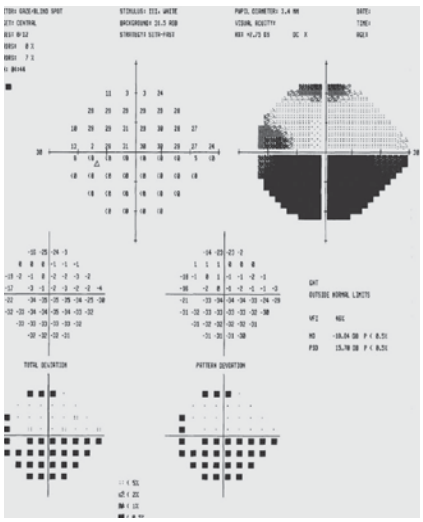

Photo: Justin Cole, OD, and Jarett Mazzarella, OD

Only one-fourth of participants developed visual field loss in either eye over a 20-year follow-up.

"In total, 199 participants developed optic disc POAG deterioration in one or both eyes without visual field abnormality," the authors noted in their study. "As a group, these participants had few differences from those who did not develop POAG when comparing the last-assessed visual field mean deviation or pattern standard deviation visual acuity, contrast sensitivity or foveal sensitivity. Greater functional differences might have been detected with more rigorous psychophysical, performance or electrophysiologic tests that were not performed in the OHTS."

Over the course of the study, 515 participants died, which alarmed the authors. "It is concerning that the number of participants who died and the number who developed POAG were approximately the same," they noted. "The incidence of POAG appeared to be generally linear over 20 years, with a possible modest increase in the rate of conversion after 15 years. "

The authors noted some factors that may have implicated the results. For example, participants may have a lower risk of developing POAG because volunteers in most studies may be more likely to return for follow-up visits and adhere to medication.

Kass MA, Keuer DK, Higginbotham, EJ, et al. Assessment of cumulative incidence and severity of primary open-angle glaucoma among participants in the ocular hypertension treatment study after 20 years of follow-up. JAMA Ophthalmol. April 15, 2021. [Epub ahead of print].

RECOMBINANT HERPES VACCINE EFFECTIVE BUT NOT POPULAR

While prevention can be the best medicine, sometimes the battle begins even earlier; namely, in helping those who need it to take the first step. The relatively recent recombinant vaccine for herpes zoster virus has been proven to reduce the incidence rate of herpes zoster ophthalmicus (HZO), but researchers have uncovered a low vaccination rate and highlight the public health need to increase herpes zoster vaccination in eligible patients.

To assess HZO incidence in the United States in vaccinated vs. unvaccinated individuals, the study included 4.8 million people who were age-eligible for herpes zoster vaccination (≥50 years old). Those with a diagnosis of herpes zoster or an immunocompromising condition within one year prior to study inclusion were excluded. The researchers found that 177,289 (3.7%) received two valid doses of the recombinant vaccine. The second dose was considered valid only if it occurred 30 to 210 days after the first dose.

The incidence rate of HZO was 25.5 cases per 100,000 person-years in the vaccinated group compared with 76.7 in the unvaccinated group. The overall adjusted effectiveness of the vaccine against HZO was 89.1%. The vaccinated group in the study was also older than the unvaccinated group, highlighting the need to improve vaccination efforts in eligible younger patients.

"By focusing on the ocular benefits of vaccination, clinicians could play a bigger role in the public health sphere by championing vaccination efforts to prevent a debilitating eye disease," the researchers noted.

Nevertheless, the study also could not assess waning of the recombinant vaccine's effectiveness, since it was only introduced in late 2017, and individuals had relatively short post-vaccination follow-up time. The researchers suggested a future study with a longer study period could confirm long-term effectiveness.

Lu A, Sun Y, Porco TC, et al. Effectiveness of the recombinant zoster vaccine for herpes zoster ophthalmicus in the United States. Ophthalmology. April 20, 2021. [Epub ahead of print].

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Tanning Beds Induce Ocular Surface Changes

There are a number of clinical studies demonstrating ocular surface damage from natural UV exposure, but there's limited evidence of the experience of indoor sun tanning sessions. In a new study, researchers evaluated the ocular surface clinically and at a microstructural level using *in vivo* confocal microscopy.

Female participants between ages 20 and 29 were enrolled into a study group with a history of UV indoor tanning and a control group with no prior history. The study subjects participated in voluntary tanning sessions performed with standard equipment and maintained their usual routine for eye protection. Slit lamp biomicroscopy and *in vivo* confocal microscopy were performed at baseline before undertaking a series of sun tanning sessions (10 sessions of 10-minute duration over a 15-day period), within three days and four weeks after the last session. Control group participants were examined at baseline and eight weeks later and did not participate in tanning sessions.

Sun tanning leads to clinically undetectable, microstructural changes affecting the cornea and the bulbar conjunctiva.

No clinically significant changes were observed in either group over time using slit lamp biomicroscopy; however, statistically significant differences were observed between the study and the control group for all corneal layers imaged using confocal microscopy. Characteristic cystic conjunctival lesions with dark centers and bright borders were observed in 95% of the study group before and in 100% after the sun tanning sessions.

This study found that the corneas of sunbed users had lower keratocyte and endothelial cell counts when compared with age-matched populations, but exposure to UV light also damages notably the epithelium of the cornea immediately after several tanning sessions.

"Although the overall corneal damage cannot be directly correlated to the UV damage, the short-term, reversible epithelial damage has no other common causative agent in our study group," the authors explained in their paper. "The number of conjunctival cystic lesions was greatest in the superior and inferior conjunctiva."

The study concluded that sun tanning leads to clinically undetectable, microstructural changes affecting the cornea and the bulbar conjunctiva. The long-term effect of those changes would lead to "UV aging of the anterior ocular surface," which appears to be similar to microstructural skin damage from UV exposure.

Grupcheva CN, Radeva MN, Grupchev DI. Damage of the ocular surface from indoor suntanning—Insights from in vivo confocal microscopy. Cont Lens Anterior Eye. April 8, 2021. [Epub ahead of print].

Speedy DEQ-5 Comparable to OSDI

Given the chronic nature of dry eye, it's often helpful to track symptoms over time using standardized questionnaires, but the experience can be time-consuming for patients and practice alike. The most frequently used questionnaire—the Ocular Surface Disease Index (OSDI)—contains 12 items and uses three subscales to assess dry eye symptoms.

The Dry Eye Questionnaire (DEQ-5) is a simplified version of the original DEQ, but compared to the OSDI, it has not been well studied. In a cross-sectional study conducted in Ghana, researchers compared the performance of both questionnaires.

Various statistical measures of reliability, sensitivity and specificity were used to evaluate the OSDI and DEQ-5 questionnaires. The reliability of the overall OSDI and DEQ-5 scores were 0.919 and 0.819, respectively. The authors noted the DEQ-5 questionnaire had good concurrent validity, based on the relatively strong correlation between its overall score and the overall score of the OSDI questionnaire.

"However, there wasn't a perfect correlation between the two questionnaires, indicative of the fact that either questionnaire might capture unique aspects of dry eye disease that the other might not," the authors explained in their study. "An imperfect correlation between the two questionnaires was expected, owing to the difference in the structure and content of the two questionnaires. The OSDI questionnaire only measures frequency of dry eye symptoms and their effects on vision-related functioning. The DEQ-5 questionnaire, in addition to assessing frequency of dry eye symptoms, is also sensitive to dry eye symptom intensity."

Despite this, the authors concluded the performance of the DEQ-5 questionnaire in discriminating symptoms of dry eye is comparable to the OSDI. The DEQ-5 questionnaire is a valid measure of dry eye symptoms and can be used as a dry eye symptom assessment tool in both studies and in practice, they argued.

Akowuah PK, Adjei-Anang J, Nkansah, EK, et al. Comparison of the performance of the dry eye questionnaire (DEQ-5) to the ocular surface disease index in a non-clinical population. Cont Lens Anterior Eye. April 6, 2021. [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.

References: 1. ZERVIATE [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals LLC; 2018. **2.** 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. **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.

eyevance pharmaceuticals

ZER-21-AD-106-02

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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ZER-04-20-MS-44

Excessive Screen Time Causes MG Atrophy

The short focal lengths and decreased blink rates that stem from digital screen use among children have been a growing concern for quite some time, predisposing kids to both myopia and dry eye. The COVID-19 pandemic certainly hasn't helped this issue, as lockdowns increased screen use—especially for those who transitioned to remote learning.

Researchers recently investigated the link between devices and dry eye further, in a study of 172 children (age six to 17). They found that children's excessive electronic screen use is associated with severe meibomian gland atrophy, with 86% of such patients reporting four hours or more of daily electronic screen use and 50% reporting over eight hours. Electronic screen use was positively associated with increased (or worse) meibography scores.

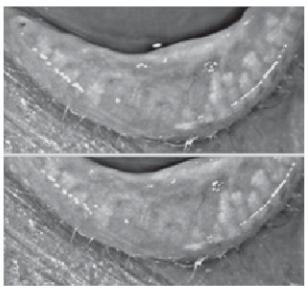

Photo: Paul M. Karpecki, OD

Electronic screen use was positively associated with increased (or worse) meibography scores.

Also, 62.5% of severe meibomian gland atrophy cases tested positive for autoimmune biomarker(s), including al-most 20% for rheumatoid arthritis, though none had systemic symptoms.

"We hypothesize underlying autoimmune disease biomarker positivity increases the risk of severe meibomian glands in those who also use electronic screens excessively due to a possible additive effect of decreased blink rates," the authors explained in their study. "Patients with autoimmune diseases, such as Sjögren's syndrome, can develop immune-mediated damage to the lacrimal and salivary glands resulting in severe dry eye. Similarly, immune-mediated damage to the meibomian glands has been reported in patients with autoimmune diseases."

The authors suspect early fibrosis and scarring of meibomian gland structures may result in more severe atrophy in patients with autoimmune diseases and increased electronic screen use due to decreased blink rates. Children in particular may benefit from preventative measures, such as using warm compresses and blinking exercises to offset low blink rates' damaging effects on the meibomian glands.

They also added that further research is needed to establish formal electronic screen use limits based on meibography grade and to evaluate the correlation of autoimmune disease biomarker positivity in children with severe meibomian gland atrophy.

Cremers SL, Khan A, Ahn J, et al. New indicator of children's excessive electronic screen use and factors in meibomian gland atrophy. Am J Ophthalmol. April 12, 2021. [Epub ahead of print].

INTRODUCING

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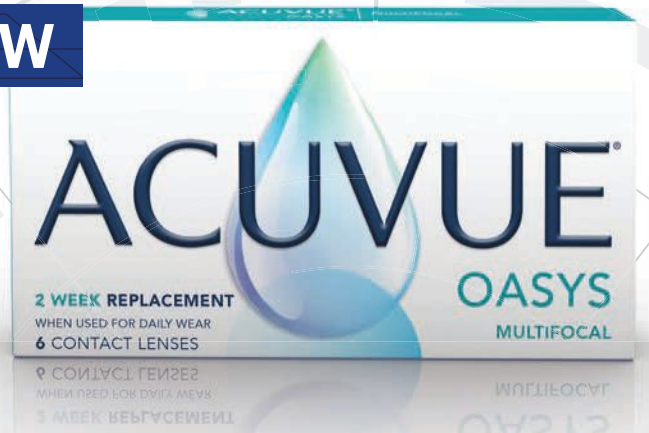

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*Compared to leading competitors' designs; technology optimized for both the parameters of refractive error and ADD power.
**www.clinicaltrials.gov is a website maintained by the NIH. The 25 clinical studies evaluated subjective comfort as a primary or secondary endpoint for ACUVUE® OASYS Brand 2-weekly and ACUVUE® OASYS with Transitions™ Light Intelligent Technology™. Review conducted as of November 12, 2020.
References: 1. JJV Data on File 2020. ACUVUE® PUPIL OPTIMIZED DESIGN TECHNOLOGY: JJVC Contact Lenses, Design Features, and Associated Benefits. **2.** JJV Data on File 2014. 1-DAY ACUVUE® MOIST MULTIFOCAL Designed for the Aging Eye.

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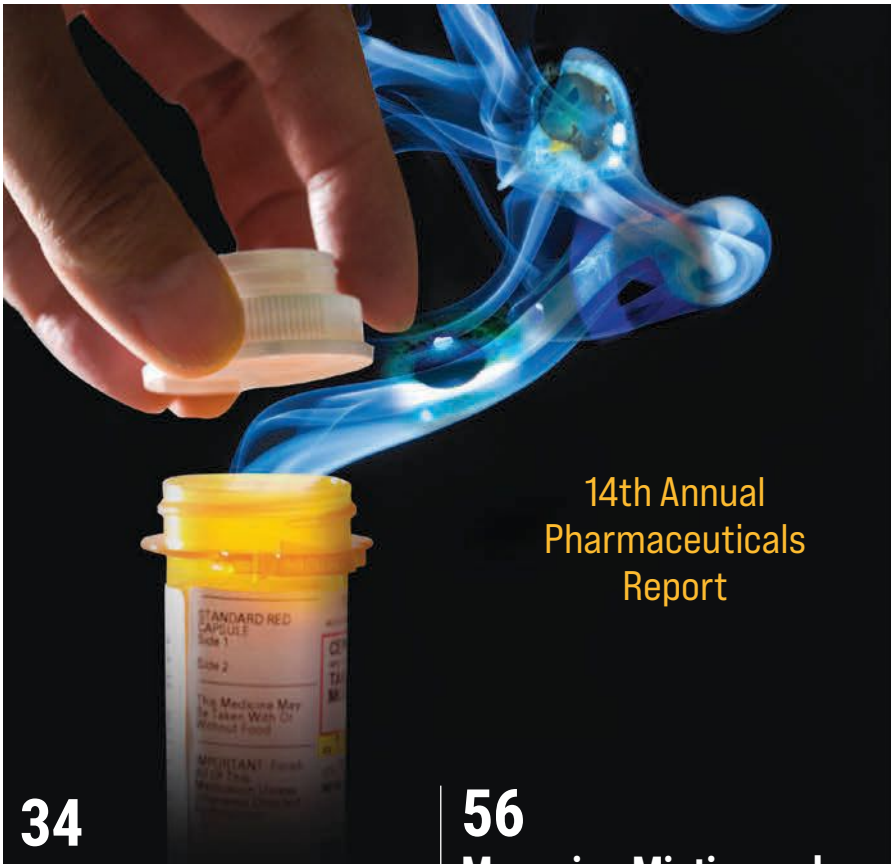
FEATURES

REVIEW OF OPTOMETRY • Vol. 158, No. 5 • MAY 15, 2021



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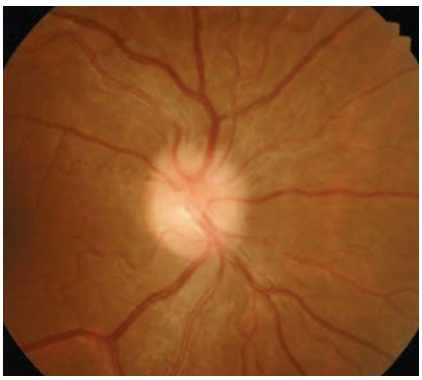

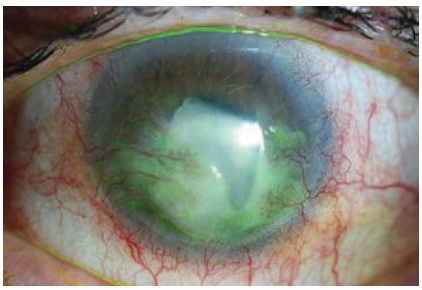

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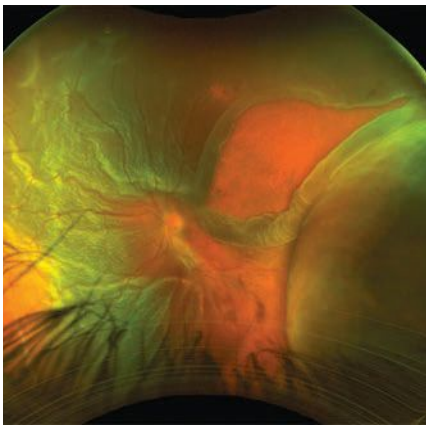

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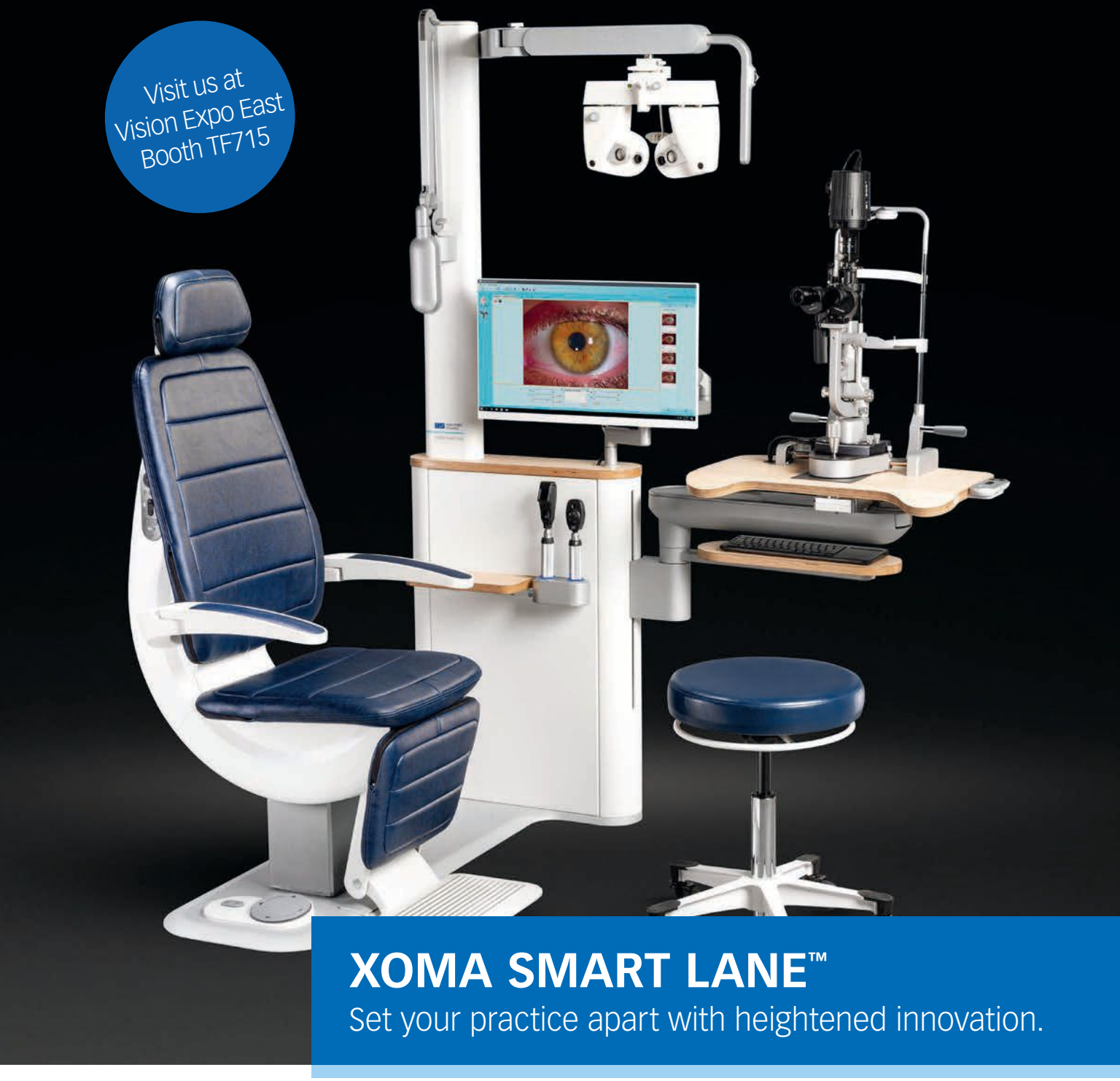

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Founded 1891
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BY JACK PERSICO
EDITOR-IN-CHIEF
OUTLOOK

The Force Awakens

In-person conferences are coming back, slowly and fitfully, but with momentum and goodwill on their side.

Those of us who are regular travelers on the educational conference circuit will probably always think of SECO 2020 when we reflect on the COVID pandemic lockdown. That was the last big meeting to happen before the profession, and pretty much the entire world, retreated from society for a year or so.

This magazine hosts a big reception at SECO each year, where over 100 people gather to talk and eat and laugh together, elbow-to-elbow, for three hours. You couldn't ask for a more convivial atmosphere. Less than two weeks after last year's event, I was literally wearing surgical gloves and a mask in the grocery store. Quite a 180 from SECO!

So, like many others, I was encouraged to see SECO's 2021 meeting happen live in-person. Kudos to them for putting in the tremendous additional effort it took to pull it off (on top of the already heavy lift of running a large, complex meeting). Organizers heeded all the necessary protocols to ensure a safe event. Attendees dutifully wore masks and abided by the social distancing requirements. It all looked very functional—but, without the personal connection, more somber this year. The evident desire to be back together ran smack into the reality that the pandemic circumstances, while much improved, are not yet resolved.

Our editorial staff produced the daily newspaper for SECO 2021, as we have for many years. Like the conference itself, we used a hybrid approach. Our publisher and sales team were in Atlanta; the editors were working from home, viewing video feeds of the presentations and reporting remotely.

I have to admit that streaming the lectures to my living room was awfully convenient, but it wasn't always engrossing. In fact, it felt a lot like watching TV: comfortable, passive and prone to distraction. Emails and texts, social media feeds and a boisterous five-year-old son who knows no work/home boundaries all competed with SECO for my attention. The *content* was as great as always; my couch potato experience, not so much.

TV binge-watching exploded during the pandemic as people found themselves with few options for their leisure time. Turn on the TV or flip open your laptop and hundreds of choices are instantly at your fingertips. But so are all the others if your attention drifts.

The day SECO ended, the ARVO conference began—all virtual this year. Just another TV show to watch.

Contrast TV with the experience of seeing a movie—critically, in a theater. That's an immersive, compelling experience that you actively must create for yourself by traveling to the location and making other logistical arrangements. A night out at the movies used to sometimes feel like a chore. (Childcare hassles! Overpriced popcorn!) And yet, that's what people seem to really crave after 14 months of isolation.

All year, it's been an open question of whether or not in-person meetings will rebound once safety concerns abate. Streaming CE's convenience, some say, demands inclusion regardless. Maybe so. It got us by when we needed it. But in-person shows feel like the movie-going experience now, and I think many post-pandemic events will be blockbusters. As Siskel and Ebert used to sign off: I'll see you at the movies. ■

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References: 1. Torkildsen GL, et al. *Clin Ther.* 2008;30(7):1272-1282. doi:10.1016/s0149-2918(08)80051-3 **2.** Data on file.

BAUSCH + LOMB

BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

Dose Escalation

A number of new and exciting pharmaceuticals to help manage ocular disease are on the horizon. Get to know them here.

We're currently in a growth phase for pharmaceutical management of eye disease. In the last month, two companies announced positive Phase III results on novel drugs for dry eye/MGD and allergic conjunctivitis. The newest FDA-approved drugs include a drop for ptosis and dry eye flares, an infusion therapy for thyroid eye disease and a glaucoma implant. Getting to know these new meds can greatly improve your care of ocular disease patients.

Two Future Therapies

Bausch + Lomb, with partner Novaliq, announced top-line results from the first Phase III trial of NOV03. This perfluorohexyloctane agent works to solubilize lipids for the treatment of MGD and evaporative dry eye disease (DED). It achieved a statistically significant improvement over vehicle for both signs (total corneal staining) and symptoms (eye dryness score). Most impressive: improvement on both measures was noted as soon as day 15.

Even more recently, and closer to FDA approval, Aldeyra Therapeutics announced a novel allergy medication called reproxalap. Reactive aldehyde species levels are highly elevated in allergic conjunctivitis and dry eye disease. Positive, statistically significant top-line results from the Phase III clinical trial were observed in the primary pre-specified endpoint and all secondary endpoints. In the last 20 years, only the steroid Alrex has achieved a sign-and-symptom label for allergic conjunctivitis.

Eysuvis for Dry Eye Flares

Having an FDA approval for dry eye flares using this new agent from Kala in is not only significant in helping DED patients but also validates our long-standing approach to the management of this disease. The approval provides us an on-label loteprednol 0.25% eye drop for short-term therapy that improves dry eye signs and symptoms. In fact, 91% of patients on chronic immunomodulators admit to experiencing flares and the average dry eye patient has between four and six of such incidents per year.

> **"Decompression surgery is painful and difficult, so having a highly effective (though pricey) alternative treatment has done wonders for patients with TED."**

Blepharoplasty in a Bottle

Shy of surgical options, there was little that could be done to improve the appearance or functioning of a ptosis. Upneeq (oxymetazoline 0.1%) was recently FDA-approved as a once daily drop for the treatment of acquired blepharoptosis. It is an α1 and partial α2 adrenergic agonist capable of contracting Müller's muscle. The treatment elevated the upper eyelid about 2mm and statistically improved the superior visual field, making this therapy an effective nonsurgical treatment for upper lid ptosis.

Thyroid Eye Disease

Another 2020 approval was Tepezza (teprotumumab-trbw) from Horizon Therapeutics for the treatment of thyroid eye disease (TED). The treatment involves a series of eight infusions of a human monoclonal antibody and a specific growth factor receptor inhibitor. It is the only therapeutic for this indication. Prior to Tepezza, patients experienced the severe repercussions of Graves' ophthalmopathy, including eye dryness, proptosis and eventual nerve compression, along with the negative cosmesis associated with TED. Decompression surgery is painful and difficult, so having a highly effective (though pricey) alternative treatment has done wonders for patients with TED.

Sustained-release Bimatoprost

The FDA also approved Allergan's Durysta (bimatoprost) implant in 2020. An inserter placed at the limbus allows the eyecare provider to easily deliver a biodegradable, sustained-release glaucoma implant into the anterior chamber. The device sits in the lower angle and is evident for about three months before dissolving. What has been interesting is that a lowered IOP equivalent to using topical drops remains for between 18 and 24 months. This treatment is ideal for many patients, particularly those with dexterity issues or ocular surface disease.

There are numerous exciting and effective pharmaceuticals at our disposal, including new mechanisms of action and first-in-class therapeutics. They can greatly help our patients with ocular surface disease, glaucoma, TED and even ptosis. It's time to get familiar with these new medications that go far in helping us effectively manage our patients. ■

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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BY MONTGOMERY VICKERS, OD

CHAIRSIDE

Looking to Be a Trendsetter? Yeah, Me Too

I may not have a million followers on Instagram—or even have an account—but I do know a thing or two about things.

Anyone who knows me knows I am not at all trendy. Perhaps that's what has stifled every one of my attempts to become a social influencer, which I'm told is a thing these days. Even though all you have to do to be a social influencer is *say* you are a social influencer, I still cannot succeed as one. That tells you something.

So, it should come at no surprise at all that no one comes to me to learn about the latest trends in optometry (or in any other area of interest for that matter, although I do know a lot about sneaking cookies past my wife).

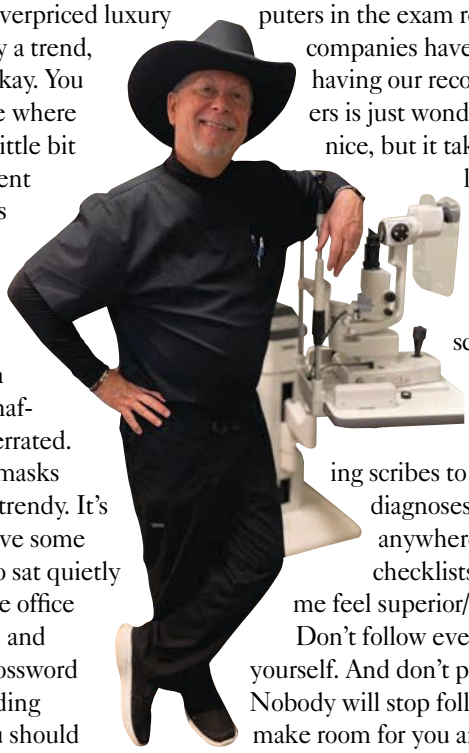
Still, I am undeterred. My crack team of investigators assures me the list of trends I've put together is "in," so here are "our" findings:

1. There is a growing glut in IT. Every freakin' kid in the universe is going to school to study IT. The more IT professionals there are, the less they'll be paid. Perhaps your kid should be a plumber. That's the next trend because who wants to fix toilets? People who want to get rich, that's who.

2. In spite of our every attempt to keep patients from making grave errors, giant glasses are coming back. It's a trend. What's next? Crown glass? Executive trifocals in a +7 hyperope? Say goodbye to each of your patient's nose and ears.

3. ODs share a similar mindset by thinking the only thing we have to do to stay in the game is have a full-service website. This trend was started by folks who want you to pay them to develop and maintain your full-service website. Smart people. Trendy people. Now, websites are better than phone books, but they still need to hold a millennial's attention for longer than the time it takes them to check a text while driving on (and sometimes off) the interstate. But this whole trend of scheduling, buying and sometimes even having an eye exam through a website is just plain creepy. I can't practice in Florida, but someone in Florida can check my Texas patient's eyes and sell them glasses and contacts! Where's the Board?

4. Leasing cool, overpriced luxury vehicles is definitely a trend, even for ODs. It's okay. You should get to decide where to spend whatever little bit of cash our benevolent government decides you get to keep (for now). But I always thought living in a hut to give off the illusion that you can afford to drive an unaffordable car was overrated.



5. Wearing more masks than anyone else is trendy. It's hard for me to believe some 80-year-old guy who sat quietly for 50 years in a little office in Washington, DC, and was paid to work crossword puzzles is now trending because he says you should wear a whole bunch of masks. You have to admire his patience. So, load up. Cover up. All the cool kids are doing it.

6. Speaking of pandemics, I got my two vaccines. They may be protecting me, but more important is that they're also a trend. "You haven't had your vaccines? Ewwwww!" Feeling superior to others is the first step to feeling trendy.

7. I've noticed if a patient opts out of widefield fundus photography and chooses dilation instead, they tend to not buy from your optical. Then they have to see you again before they leave the office, taking up more valuable time and resources and offering next to nothing in return. It's your call, but I would urge you to strongly encourage them to come in yearly. And I personally would never be so presumptuous as to pre-appoint them. They'll call, right? By the way, three or four drops of atropine really dilate well.

8. I guess the use of scribes is a trend. You see, we all have our charts on computers in the exam rooms. Marketing companies have convinced us that having our records on computers is just wonderful. It is kinda nice, but it takes us twice as long to complete the chart so we need scribes to get it right. I like having scribes for scribe purposes and to blame dilation issues on (see #7). I also like having scribes to see if I can find diagnoses that aren't found anywhere in the EHR checklists they use. Makes me feel superior/trendy.

Don't follow every trend. Be yourself. And don't post stupid stuff. Nobody will stop following Dua Lipa to make room for you anyway. ■

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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†Compared to a single vision 1 day lens over a 3 year period.

1Chamberlain P, et al. A 3-year randomized clinical trial of MiSight® lenses for myopia control. *Optom Vis Sci.* 2019; 96(8):556-567.

Blindsided

A thorough, dilated examination of the retina is necessary to diagnose retinitis pigmentosa.

Q A 32-year-old mother of three came in for a routine exam with no complaints. Vision was 20/20, but confrontation fields were dramatically constricted. The fundus exam confirmed retinitis pigmentosa (RP). How do I deliver the news, and what are the next steps?

A "Breaking this news to patients is often more of a challenge than reaching the proper diagnosis," says Chelsea Miller, OD, of Athens Family Vision Clinic in Athens, GA. In many RP patients there is a known history, and family members have a clear understanding of the condition and its inheritance pattern. However, in a patient like ours, who presented for a routine eye exam, this conversation can be a lot more difficult.

After discussing a potentially devastating diagnosis like RP with a patient, Dr. Miller believes ongoing support is important. They will have more questions after they do their own research. "In my experience, let the patient know that you are available to answer any further questions via phone, email or future appointments," she recommends. "Patients who know their eye care provider is reliable and accessible will be very appreciative."

RP Refresher

Retinitis pigmentosa is a progressive condition that causes retinal degeneration at the photoreceptor level. It affects rods initially and more severely than cones. Vision loss will begin in the periphery and gradually progress into the central vision, where rods are less dense. Because rods are more affected, complaints of difficulty seeing in dim/dark lighting are common. In its end stages, RP can also causes a loss of cones and affect central vision and best-corrected visual acuity. The inheritance pattern can be autosomal dominant (30% to 40%), autosomal recessive (50% to 60%) or X-linked recessive (5% to 15%). RP can also be associated with Leber's congenital amaurosis and Usher syndrome.[1]

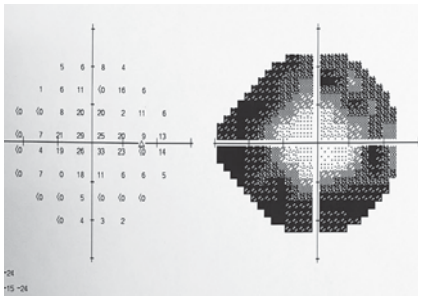

Fig. 1. VF reveals peripheral vision loss.

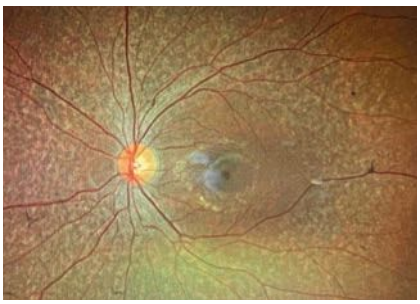

Fig. 2. Bone spicules are a common finding of most RP patients.

A thorough, dilated retinal examination can determine if there is any alteration in pigmentation and also detect the presence of bone spicules, a common finding in RP patients. Considering the degree of field loss (*Figure 1*), there were few bone spicules noted in this case (*Figure 2*).

Comanaging with a retina specialist is not always necessary. However, documenting the degree of vision and visual field loss as a baseline is critical to monitor progression. Fundus photos, visual field testing and electrodiagnostic testing if available are other essential components of diagnosis, according to Dr. Miller.

Electroretinograms (ERGs) measure the electrical response of the photoreceptors and can help detect early disease as well as distinguish between retinal disease and optic nerve disease. The multifocal ERG can measure responses in the fovea, which is more beneficial in later stages of RP.

Testing Responsibilities

Referring a patient and their family members for genetic testing is important. "The genetics of RP can vary, and testing by a trained counselor may offer information in terms of inheritance patterns and gene mutations as well as a prognosis," Dr. Miller says.

There are risks and benefits to predicting the future of RP in asymptomatic family members without clinical signs—either a false sense of security that they will never get it or a lifetime of fear that they will. One pro to genetic testing in children of RP patients is that it may qualify them for clinical trials. Gene therapy research for certain types of RP is currently underway, giving hope to patients in the future.[2]

In this specific case, genetic testing was performed using the patient's saliva, which confirmed RP and will also help determine the risk factors for her children. ■

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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. He has no financial interests to disclose.

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BY BISANT A. LABIB, OD

Surveying the Cavern

Take a closer look at how the features that make up this sinus function—and can lead to dysfunction.

The eye is an extension of the brain and central nervous system. Through a simple ocular examination, we can glean significant insight into complex neurological processes. Ophthalmologic examinations thus serve as conduits through which we can detect and diagnose many underlying neurologic conditions.[1]

One of the anatomic conduits that connects the eye to the brain is the cavernous sinus. This structure is one of two paired intracranial dural venous sinuses located posterior to the orbit and on either side of the sella turcica of the sphenoid bone. Anteriorly, the cavernous sinus communicates directly with the superior and inferior orbital fissures and indirectly with the pterygopalatine fossa.

Its primary function is the transport of deoxygenated blood. As such, it communicates with numerous venous structures, including the superior and inferior ophthalmic veins, basal venous plexus, superficial middle cerebral vein and superior and inferior petrosal sinuses.

The cavernous sinus is so much more than a simple vein. Many important neurovascular structures travel through it due to its location between the orbit and brain proper. These include the internal carotid artery (ICA), cranial nerve (CN) III, CN IV, two divisions of CN V (1 and 2) and CN VI. All the constituents of the cavernous sinus are related to and have an effect on ocular function.[2] As such, it is important we understand them.

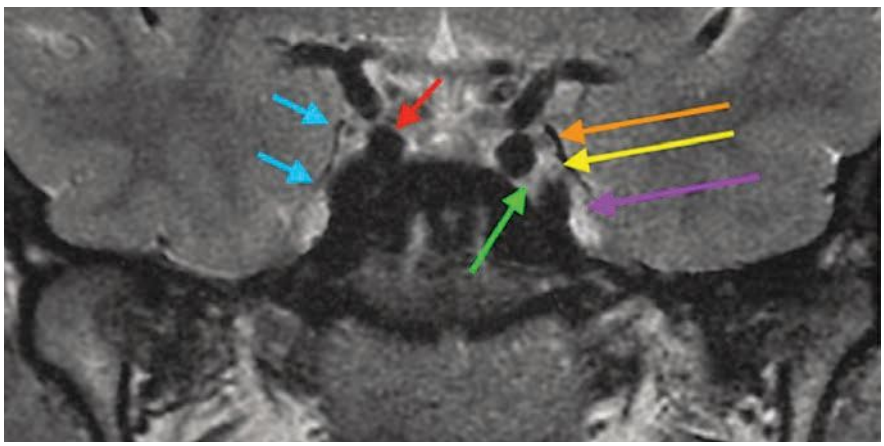
Deep Dive

Often, observable ocular abnormalities on clinical exam aid in identifying the source, if not also the etiology, of a patient's condition. Here's what disruptions to the features of the cavernous sinus look like and tell us.

ICA. The common carotid artery (CCA) arises directly from the aorta on the left and indirectly on the right through the brachiocephalic artery. The CCA bifurcates within the neck, giving rise to the ICA, which continues intracranially and gives off several smaller branches.[3] Surrounding the ICA are postganglionic, sympathetic fibers. The sympathetic system affects many ocular structures and is responsible for innervating the superior tarsal muscle of the upper eyelid and the pupil dilator. Sympathetic disruption may occur in cavernous sinus disease, allowing the parasympathetic system to dominate, resulting in a miotic pupil and ptosis. These features, with the addition of anhidrosis on the affected side, constitute Horner's syndrome.[4]

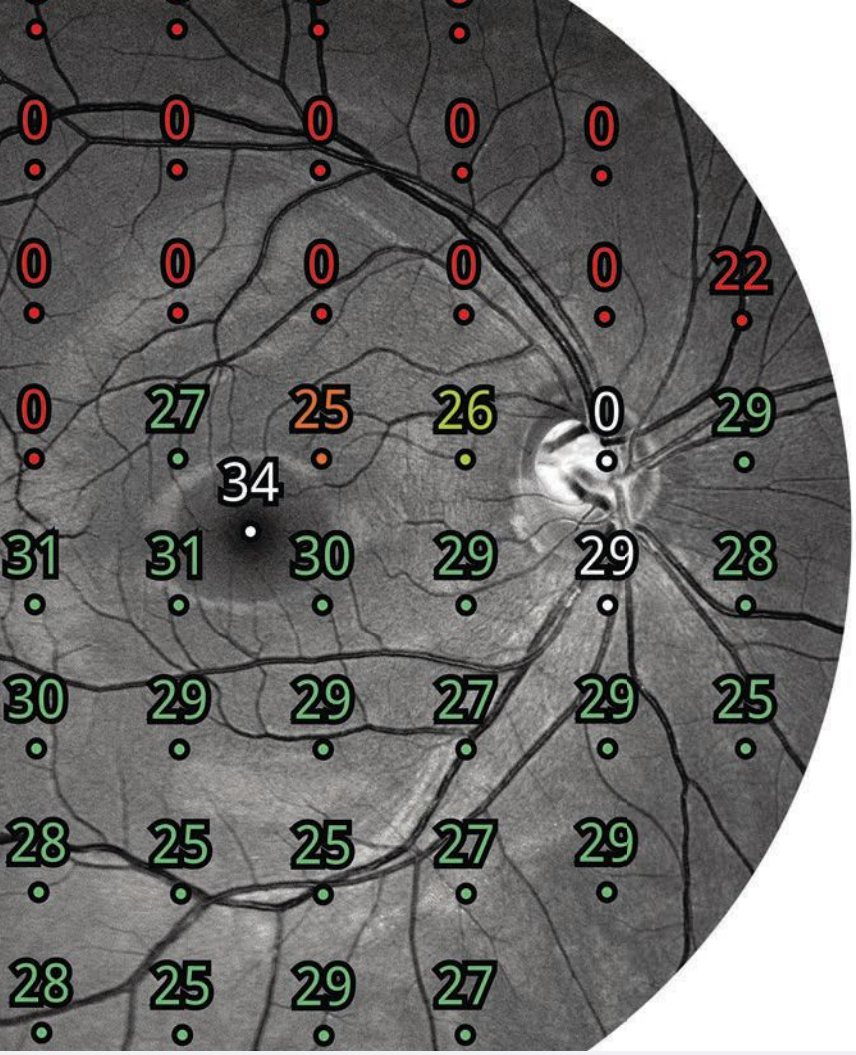
Oculomotor nerve (CN III). Running along the superior-lateral wall of the cavernous sinus is CN III. In conjunction with the aforementioned sympathetic stimulation of the upper eyelid, CN III innervates the levator palpebrae superioris, contributing to the majority of eyelid elevation. Additionally, it innervates many ocular muscle branches, such as the superior rectus, inferior rectus, medial rectus and inferior oblique. Fibers also extend to the pupillary sphincter. As such, a lesion in the cavernous sinus affecting the third nerve causes ptosis that is more significant than in sympathetic dysfunction.

Additionally, patients may have a resting position where their eye is sitting "down and out" due to the lack of muscular innervation. If pupil involvement is present, dilation would be evident. A patient with CN III palsy may report symptoms of diagonal, binocular diplopia and a drooping eyelid, among other side effects.[5]



MRI imaging of the brain through the cavernous sinus shows the lateral border of the right cavernous sinus (blue), cavernous segment of the right ICA (red), left CN III (orange), left CN IV (yellow) and left CN VI (green). The left CN V-1 and left CN V-2 are not well resolved (purple).

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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Trochlear nerve (CN IV). Subadjacent to CN III within the lateral wall of the cavernous sinus is CN IV. This nerve, after exiting the cavernous sinus, continues on its course to eventually innervate the superior oblique (SO) muscle. The SO is the sole extraocular muscle that is innervated by CN IV and functions primarily as a depressor. Secondary and tertiary functions include abduction and intorsion of the eye. Patients with SO palsies may report vertical or diagonal diplopia that is worse on downgaze. They may also have a compensatory head tilt to balance out the torsional effect.[6]

Trigeminal nerve (CN V). CN V consists of three branches on either side to provide sensory and motor function to the entire face. Only the first two of these branches, the ophthalmic (V-1) and maxillary (V-2), are contained within the inferior aspect of the cavernous sinus. These two divisions are primarily sensory in function. The ophthalmic division provides sensory innervation to the orbital and supraorbital portion of the face. It also supplies various ocular structures, such as the lacrimal gland, ciliary body, cornea and conjunctiva. The maxillary division innervates the infraorbital portion of the face above the mouth, as well as the maxillary teeth and sinuses.

Cavernous sinus pathology that affects the area housing these branches reduces sensation on the ipsilateral side of the face.[7] This can be tested clinically using the end of a tissue or cotton wisp to stroke the area of distribution on either side while the patient has their eyes closed, to check for symmetry.

Abducens nerve (CN VI). Cranial nerve VI is responsible for the abduction of the eye. It is the most medially positioned cranial nerve within the cavernous sinus, located just slightly inferior to the cavernous ICA. After exiting the cavernous sinus, it eventually innervates the lateral rectus muscle within the orbit.

Patients with CN VI dysfunction may report horizontal, binocular diplopia due to their inability to abduct the eye.[8]

The Function and Dysfunction of Cavernous Sinus Structures

Structure	Ocular Function	Ocular Dysfunction
ICA	· Superior tarsal muscle of upper eyelid · Pupil dilator	· Horner's syndrome (miosis, small ptosis, anhidrosis)
CN III	· Levator palpebrae superioris · Superior rectus · Inferior rectus · Medial rectus · Inferior oblique · Pupillary sphincter	· Larger ptosis · Diagonal binocular diplopia · Mydriasis
CN IV	· Superior oblique	· Diagonal binocular diplopia worse on downgaze · Head tilt
CN V-1	· Sensory input orbital and supraorbital portion · Ciliary muscle · Lacrimal gland · Conjunctiva · Cornea	· Decreased sensation of the forehead and above the eye
CN V-2	· Sensory input to infraorbital portion extending above the mouth	· Decreased sensation below the eye to above the mouth
CN VI	· Lateral rectus	· Horizontal binocular diplopia

Take-home Message

With a clear understanding of cavernous sinus anatomy, we can see how pathology in and around the structure leads to a myriad of ocular manifestations. These pathologic conditions of the cavernous sinus typically fall into one of four categories: vascular, tumor, trauma or inflammation.[2] Vascular conditions include aneurysms arising from the cavernous ICA or venous thrombosis of the cavernous sinus itself. Numerous tumors may arise from or invade the cavernous sinus, including schwannoma, meningioma, extramedullary plasmacytoma, pituitary macroadenoma and metastasis.[9] Trauma may lead to the formation of a cavernous-carotid fistula. Finally, inflammation may affect the cavernous sinus in the form of idiopathic orbital inflammation, also called Tolosa-Hunt syndrome.[2]

Pathology within the cavernous sinus can lead to many vision-threatening scenarios. But more than that, these ocular signs and symptoms may often be the initial heralds of a life-threatening cavernous sinus syndrome. It is imperative to identify and appropriately work up suspected cavernous sinus pathology with timely diagnostic neuroimaging and referrals.

In the event that multiple cranial nerves are implicated on clinical examination, it is necessary to keep in mind this specialized intracranial compartment. ■

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BY JOHN RUMPAKIS, OD, MBA
CLINICAL CODING EDITOR

Spring Renewal

With the change of the seasons comes opportunity.

Spring hits different this year—one can sense the feeling of renewal and optimism that comes with the rollout of the COVID vaccines and communities reopening. How different from last year. One thing, however, isn't different. Springtime in the world of eye care brings another feeling: the itch and discomfort of ocular surface disease (OSD).

Beware Allergy Season

OSD is a broad and common presentation in our offices. We often think about dry eye when we hear OSD, but don't forget that OSD incorporates lid disease as well as other conjunctival and corneal issues. OSD also often occurs with other disease states, such as ocular allergy. When we think about proper diagnosis and treatment of the entire ocular surface, it is critical that our medical record keeping maintains proper detail to support our billings.

Understanding the fundamentals of determining the proper type of medical office visit (920XX or 992XX) is essential for proper medical record compliance and patient management. While some conditions that we treat, such as seasonal allergies, are acute, many are chronic and require continuing care. Set expectations with these patients, as this is not a one- or two-visit process but ongoing management. By most OSD protocols, you may be seeing this patient two to four times per year in addition to their general refractive care.

Proper Protocol

The chief complaint becomes the epicenter of our medical record when coding for ocular surface disease. Keep in mind that the CC must be stated in terms of "complaints or symptoms of an eye disease or injury" to meet the standard of invoking a patient's medical insurance benefits, and we want to be specific about these signs and symptoms particularly since we may be diagnosing and treating multiple concurrent conditions. If providing a physician-directed return office visit, the CC should be implicit; *e.g.*, "patient returning for physician directed visit secondary to findings consistent with (insert signs and symptoms here)."

> **While some conditions, such as seasonal allergies, are acute, many are chronic and require continuing care.**

Once the CC requirement has been met, then you can proceed with your evaluation. Be mindful that the level of the office visit must be proportional to the level of the disease state. Never assume or code an office visit based upon the patient diagnosis but rather on the medically necessary individual components that you performed. Don't forget: with the change in 2021 E&M coding rules, you can choose to use either total time or medical decision making to determine the office visit level.

When differentiating between a 920XX code and a 992XX code, a 92012 requires that the patient present with a new condition or an existing condition complicated with a new diagnostic or management problem not necessarily relating to the primary diagnosis. If that isn't the case, a 992XX code is the way to go. The new E&M code definitions make coding much easier since we have to provide a "medically appropriate history and examination," but they can complicate the medical necessity requirements since it is now more subjective.

Personally, I prefer the 992XX codes for medically related eye care visits. Think of them as structure- and function-based coding hierarchy rather than the general overall evaluation a 920XX code provides. Always code each patient encounter by the individual case presentation, as well as the individual patient you are examining and treating, using the choices that you have using either total time or medical decision making as your coding criterion.

When doing ancillary testing, most of the additional tests that you perform will be incidental to the office visit and not separately billable. Measuring tear volume whether by evaluating the meniscus or by Schirmer are not separately billable procedures. Standing orders for clinical lab tests for inflammation (MMP-9) and tear osmolarity are common if the patient has documented signs and symptoms from a qualified questionnaire. However, adjunctive items like photos, lid debridement and meibography must have a clear path of medical necessity established in the record in order for them to be legitimately performed—and don't forget the interpretation and report requirement with any special ophthalmic testing.

Diseases that affect the ocular surface can be seasonally acute or chronic, but pollen isn't the only thing in the air this spring—it's optimism and opportunity. ■

Send your coding questions to rocodingconnection@gmail.com.

About Dr. Rumpakis

Dr. Rumpakis is president and CEO of Practice Resource Management, a firm that provides consulting, appraisal and management services for healthcare professionals and industry partners. As a full-time consultant, he provides services to a wide array of ophthalmic clients. Dr. Rumpakis's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

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STAY ALERT FOR SYSTEMIC MED SURPRISES

Many ocular adverse effects may be hiding inside your patient's pill bottle. Here's a new way to think about them.

AARON CASE, OD
FORT WAYNE, IN
JOY KERNS, OD
WYOMING, MI
SARA WEIDMAYER, OD
GRAND RAPIDS, MI

The list of systemic drugs that may have ocular effects is enormous. While perusing a patient's medication list and considering all the possible effects can be daunting, it is important to be watchful and educate the patient about any concerning ocular complications that could potentially arise. However, rather than the typical "this medication can cause these effects" mentality, it's often more clinically relevant to think of it the other way around: "With this clinical finding, could one of the patient's medications be causing the problem?" This sort of *effect→cause* rather than *cause→effect* thinking can help you when you're confronting a clinical finding in your chair and need to think backwards to determine the source.

Here, we'll touch on some of the more commonly encountered ocular side effects related to systemic meds, grouping the findings by ocular location or function to help allow that "retrace your steps" approach to connecting presentations to medications.

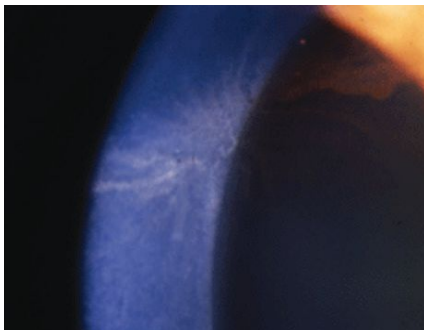

Photo: Jay Pepose, MD, PhD

Fig. 1. Amiodarone causes corneal whorl keratopathy, or corneal verticillata, visible at the level of the basal epithelium.

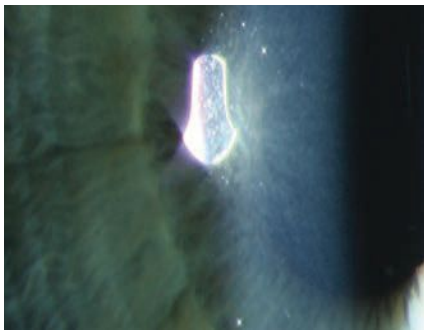

Photo: Sara Weidmayer, OD

Fig. 2. Early subepithelial refractile deposits in a patient on macrolide therapy for chronic obstructive pulmonary disease.

Cornea

Some of the most readily apparent effects of systemic meds appear in the cornea, given the structure's ease of observation to patient and doctor alike. Many drugs allow drug penetrance into cells with the potential for phospholipid accumulation intracellularly. This manifests in the eye as vortex (or whorl) keratopathy (*Figure 1*). The finding starts at approximately three weeks and is generally reversible within months of discontinuation of the medicine. Vortex keratopathies rarely have any effect on acuity but can cause blurry vision or, on rare occasions, even corneal ulceration. Drug-related keratopathies generally resolve with discontinuation of the offending agent.

Drugs causing vortex epithelial deposits include amiodarone, hydroxychloroquine, chlorpromazine, tamoxifen, nonsteroidal anti-inflammatory drugs, atovaquone, suramin, perhexiline maleate and aminoglycosides.[1]

About the authors

Dr. Case is an attending and residency director at the Fort Wayne VA NIHCS Eye Clinic, an adjunct assistant professor with Indian University and a clinical associate professor with the Michigan College of Optometry. **Dr. Kerns** practices at the Wyoming VA Community Based Outpatient Clinic in Wyoming, Michigan, and is on clinical faculty for the Michigan College of Optometry, Illinois College of Optometry and Pennsylvania College of Optometry. **Dr. Weidmayer** practices at the VA Ann Arbor Healthcare System and is a clinical assistant professor for the University of Michigan's Department of Ophthalmology & Visual Sciences. None of the authors have any financial interests to disclose.

Similarly, many drugs are subject to lysosomal sequestration or drug precipitation, which can lead to a crystalline keratopathy. These often begin as a diffuse punctate subepithelial deposit, which may become more linear. In contrast to whorl forms, crystalline-like keratopathies are more likely to elicit a decrease in acuity, especially when caused by antineoplastic agents.

Inciting agents include benoquine, tilorone, macrolide antibiotics, clofazimine, gold salts and multiple antineoplastic agents, including vandetanib, osimertinib, cytarabine and emtansine (*Figure 2*).[1] While discontinuing the offending agent may be impossible, it's important to identify the correlation and communicate with the prescribing physician to consider titrating to a tolerable dose.

While any topical ophthalmic drug containing the common preservative benzalkonium chloride (BAK) can independently elicit corneal edema, as can several topical antiseptics, it is a very rare complication of systemic medications. Most notably, amantadine—an anti-Parkinson's drug—has been demonstrated to reversibly provoke corneal edema in rare cases.

Lens

Early cataract formation is the most likely drug-related effect we commonly see in practice.

Phenothiazines *(chlorpromazine, thioridazine).* This is a group of psychotropic medications used to treat serious mental disorders including schizophrenia and psychoses. These drugs, specifically chlorpromazine and thioridazine, are associated with cataract formation in the anterior subcapsular layers and are nearly always associated with pigment accumulation.[2] Over time, this pigment can become arranged in a stellate pattern, but is rarely associated with visual impairment.[3] These opacities are rarely bilateral but are typically asymmetric when they are, and are not likely to reverse with cessation of the medication.[4]

Glucocorticoids. These are a group of corticosteroid hormones used to reduce inflammation and suppress the immune system. Whether systemic, topical, inhalant, nasal spray or injected, they can produce posterior subcapsular cataract (PSC) in both adults and children, and do appear to be dose- and time-dependent. While the lenticular changes may progress or remain stationary, they will rarely reverse with discontinuation of the medication. The cataract typically begins as a PSC but can gradually progress to appear similar to other types, including senile cataract.[2] Patients on corticosteroids should be educated on the possibility of cataract formation and have routine eye evaluations.

Retina

Access to the vasculature makes the retina fertile ground for complications of systemic med use.

Interferon *(Intron A, Roferon-A).* The interferons (IFNs) are glycoproteins classified as cytokines and used primarily for hepatitis C virus (HCV). Specifically, INF-α used to treat HCV that is associated with ocular manifestations.

The most common finding is INF-α associated retinopathy, predominantly with cotton wool spots and flame-shaped hemorrhages in the posterior pole radiating from the optic nerve (*Figure 3*). These findings rarely cause significant visual disturbance and may go undetected due to lack of patient symptoms. Risk factors include type 2 diabetes, systemic hypertension, increasing age and duration of treatment.

Retinal changes usually occur by week 12 of therapy but can take as long as 28 weeks to manifest. Typically, the retinopathy will resolve on its own, even with the continued use of the medication. Patients should have a baseline dilated fundus exam prior to initiating INF-α therapy, then follow-up every three to six months throughout the course of treatment. The finding of retinopathy is not typically a reason to discontinue treatment unless there's associated acute vision loss, and the retinopathy most often resolves less than one month after completion of treatment.[5]

Tamoxifen *(Soltamox).* This antiestrogen medication is used to treat estrogen receptor–positive breast cancer, ovarian cancer, pancreatic cancer and malignant melanoma.[6] The retinal findings most often associated with it include small refractive bodies in the inner retina, which appear like dot-like yellowish deposits surrounding the macula.[2] Patients may also be at risk for development of pseudocystic cavitary spaces—without macular edema—which may only be visible on SD-OCT imaging.

The OCT appearance of the condition appears very similar to that of idiopathic macular telangiectasia type 2 and has been found to occur early in treatment, at low doses of the drug; it is irreversible.[7] There is also a more severe form of retinopathy that can include cystoid macular edema, retinal hemorrhages and optic nerve edema, and is associated with vision loss. This more acute form of toxicity is most likely to occur only after a few weeks of starting therapy whereas the less severe form usually occurs after more than one year of treatment, when a total of more than 100 grams of the drug has been dosed.[6]

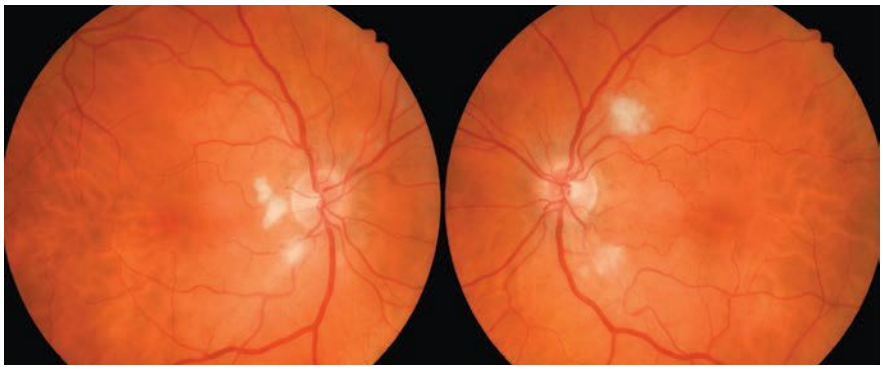

Photo: Sara Weidmayer, OD

Fig. 3. Interferon retinopathy with cotton wool spots.

Help your patients with **DIABETIC RETINOPATHY (DR)**, and

HELP DRIVE PATIENT OUTCOMES

Through early detection, monitoring, and timely referral, you can play a pivotal role in managing your DR patients' vision[1-3]

IF YOU SEE OR SUSPECT DR:

Educate your patients about living with DR and potential treatment options[2,3]

Refer DR patients for timely intervention

- According to the AOA, you should refer patients with[2,3]
  - Severe nonproliferative DR (NPDR) within 2 to 4 weeks
  - Proliferative DR (PDR) within 1 week

Follow up to ensure they have visited a retina specialist

INDICATIONS AND IMPORTANT SAFETY INFORMATION

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

References: 1. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991;98(5 suppl):823-833. **2.** Care of the Patient With Diabetes Mellitus: Quick Reference Guide. American Optometric Association website. http://bit.ly/2M22OUJ. Accessed August 7, 2019. **3.** Ferrucci S, Yeh B. Diabetic retinopathy by the numbers. *Rev Optom*. June 15, 2016. http://bit.ly/2KNNJ4E. Accessed August 7, 2019.

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EYLEA®
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For Intravitreal Injection

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Visit **diabeticretinaldisease.com** for additional information and useful patient resources

Continue to monitor your patients with DR[2,3]

- The AOA recommends frequent monitoring of patients[2]
  - At least every 6 to 8 months in patients with moderate NPDR and more frequently for patients with greater disease severity[2]

The more you know about emerging clinical science about anti-VEGF and other potential therapies for DR, the better you can help inform your patients about how treatment may be able to help

Refer patients to a retina specialist who can treat DR[2,3]

WARNINGS AND PRECAUTIONS (cont'd)

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Please see Brief Summary of Prescribing Information on the following pages.

anti-VEGF = anti–vascular endothelial growth factor; AOA = American Optometric Association.

03/2020
EYL.20.02.0082

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure.
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use.
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use.
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306

Patients should have a baseline eye exam and yearly screening with a dilated fundus examination and SD- OCT imaging. If ocular manifestations are present, it is recommended to consult with the patient's oncologist as a change in dosage or discontinuation of the drug may be indicated.[7]

***Canthaxanthine** (Orobronze).* A naturally occurring carotenoid whose oral consumption may cause bronzing of the skin, canthaxanthine is sold over the counter as a tanning agent. This substance has been FDA approved for use as an artificial food coloring agent but not for any other use.

Orobronze deposits in all layers of the retina with a preference for the more superficial layers and will appear as very small, gold-like particles near the macula.[6] The associated retinopathy does appear to be dose-dependent, and is found in 50% of patients who have taken at least 37 grams and nearly 100% of those who have consumed at least 60 grams of the drug. Most patients will be asymptomatic; however, occasionally it can cause abnormal dark adaptation. The retinal deposits do resolve with the discontinuation of the drug.[8]

Macula

Here we encounter some of the heavy-hitters most familiar to optometrists, especially Plaquenil, with which we have a long history.

***Hydroxychloroquine** (Plaquenil).* The choloroquines are a class of chemotherapeutic agents and a mainstay as both treatment and prophylaxis against malarial disease and Q fever. Hydroxychloroquine is effective in managing various autoimmune conditions, including rheumatoid arthritis, Sjögren's, lupus and porphyria cutanea tarda.

The ophthalmic complications primarily lie in its ability to produce a toxic maculopathy in a dose-dependent manner. Findings include a bull's-eye maculopathy in the late stages, associated with more subtle findings on OCT, fundus autofluorescence (FAF), multifocal electroretinogram (mfERG) and threshold perimetry findings in the early stages (*Figure 4*).

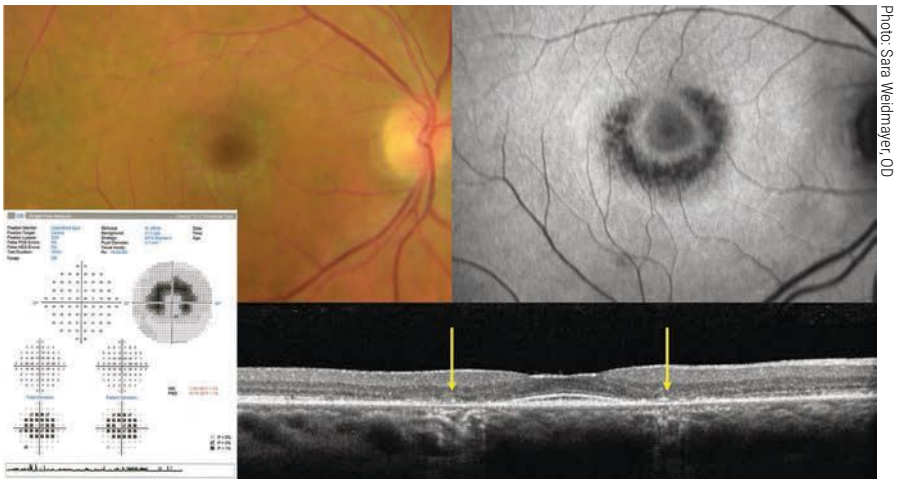


Photo: Sara Weidmayer, OD

Fig. 4. Classic advanced hydroxychloroquine-induced toxic maculopathy showing parafoveal RPE/outer retinal loss (yellow arrows on OCT), hypoAF on FAF imaging and corresponding paracentral visual field defects.

Monitoring should include a baseline exam within one year of initiating therapy, then biannual exams after five years of use including OCT and 10-2 threshold visual fields. FAF and mfERG may have utility in early detection. Early findings in OCT may show disruption of the outer ellipsoid zone and parafoveal thinning of the outer nuclear layer, which may progress to "flying saucer" sign with advanced toxicity.

FAF may demonstrate early patchy hyperautofluorescence (hyperAF) circumferentially around the fovea, which may coalesce to a ring in advanced disease. mfERG studies are sensitive but widely variable and are of limited value in isolation. Threshold visual fields will similarly show patchy shallow depressions circumferentially about the fovea which will coalesce into continuous, deeper scotomas in advanced disease.

Of note, Asian patients tend to have defects more peripherally in the macula and should be evaluated with a 24-2 visual field. The chance of retinal toxicity increases with time and has as high as a 20% risk at 20 years.[9] Concurrent use of tamoxifen increases the risk of maculopathy fivefold.

***Pentosan polysulfate sodium** (Elmiron).* PPS is an oral medication approved for the relief of bladder pain or discomfort associated with interstitial cystitis/painful bladder syndrome.

A unique pigmentary maculopathy was only recently elucidated in 2018 and has subsequently been bolstered by larger population studies. Current evidence suggests a dose-dependent pattern of damage with caution in anyone with a cumulative exposure of greater than 500g. Color fundus photos, OCT, FAF and near-infrared reflectance (nearIR) imaging are key to detection. Fundus evaluation will demonstrate yellow deposits at the level of the retinal pigmented epithelium (RPE), which correlate to hyperreflective focal RPE thickening via OCT. Similarly, these deposits correlate to hyperAF on FAF and hyperreflective patches on nearIR imaging, which show highly disorganized patterns and irregularity in excess of what might be predicted by fundus evaluation.

A hyperAF halo may be evident in the peripapillary region (*Figure 5*).[9] The clinical course and endpoints are unknown, but maculopathy can evolve after discontinuation and patients should be followed at regular intervals.

***Phenothiazines** (multiple trade names).* This drug class encompasses a larger group of antipsychotic agents in which thioridazine and chlorpromazine are the most prescribed. They have been largely supplanted by newer medications— especially in chronic therapy— but are still commonly used.

In contrast to most toxic maculopathies, the macular toxicity seen here is more dependent on daily doses rather than a cumulative one. The mechanism

Photo: Sara Weidmayer, OD

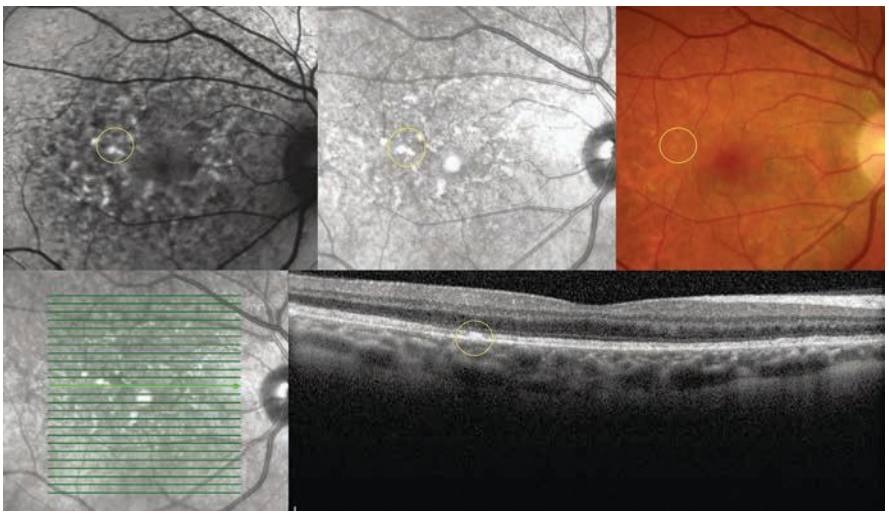


Fig. 5. Multimodal imaging demonstrating collocated yellow deposits, RPE thickening, near infrared hyper-reflectance and hyperAF on FAF imaging in advanced Elmiron maculopathy.

of damage is not completely understood, but they are thought to disrupt rhodopsin synthesis.[11]

Onset of visual symptoms typically occurs within weeks of initiating therapy in doses greater than 800mg daily of thioridazine and 1200mg daily of chlorpromazine. In the early stages, course granular pigmentation occurs, followed by patchy RPE loss with a characteristic ovoid shape extending to the midperipheral retina. In late stages, widespread areas of depigmentation and hyperpigmented plaques are visible, followed by geographic atrophy.

At most doses, benign pigmented corneal and anterior lens opacities can also occur. OCT can reveal photoreceptor loss, which may span the fovea extending far into the arcades. There is typically some measure of visual recovery upon discontinuation.[12] In standard doses, routine exams are sufficient for monitoring, while symptomatic individuals should be examined within the week. Alternate meds should be discussed with the prescribing practitioner at the first sign of toxicity.

Sertraline *(Zoloft, Celexa, Lexapro, Prozac, Paxil).* This a commonly prescribed selective serotonin reuptake inhibitor (SSRI) for depressive and anxiety disorders and more infrequently for bulimia nervosa and anorexia nervosa.

While the link between sertraline and maculopathy has yet to be firmly established, there are multiple case reports describing acute-onset bilateral maculopathies in otherwise healthy eyes following initiation of therapy at standard doses, whose findings closely mimic those in advanced hydroxychloroquine toxicity.[13] While maculopathies appear infrequently, the reported cases are profound, so be aware of this potential adverse effect given the widespread use of this medication.

Optic Nerve

As we encounter neuro-ophthalmic involvement, the potential for serious vision loss escalates.

Phosphodiesterase Type 5 (PDE5) Inhibitors *(Viagra, Levitra, Cialis).* This class of drugs is used to treat erectile dysfunction (ED). There has been an association between PED5 inhibitors and non-arteritic anterior ischemic optic neuropathy (NAION); however, there has been no evidence confirming a cause-effect relationship. The clinical picture of NAION in patients taking these medications is the same as one that occurs spontaneously: edematous and hyperemic optic disc, relative afferent pupil defect and painless loss of vision.

It's important to note that most patients who require the use of ED medications have the same risk factors (older age, vascular risk factors such as hypertension and diabetes) for NAION, which makes it very difficult to establish a definite association between the two.[2] It is recommended that these drugs be avoided in patients who have experienced NAION in one eye, as they may be more likely to develop the condition in the same or fellow eye.[6]

Amiodarone *(Pacerone).* An anti-arrhythmic drug, amiodarone is one of the most effective medications available to treat various cardiac arrhythmias.

While the exact mechanism is unknown, there is a probable association between amiodarone use and optic neuropathy. However, note that the neuropathy secondary to amiodarone use differs from typical NAION in that the condition is bilateral, associated vision loss progresses slowly over several months and the degree of vision loss tends to be less severe. The disc edema is also much slower to improve when compared to NAION, which can help distinguish between the two.

Patients on amiodarone should have a baseline exam with follow-up every 12 months, or immediately should visual symptoms occur.

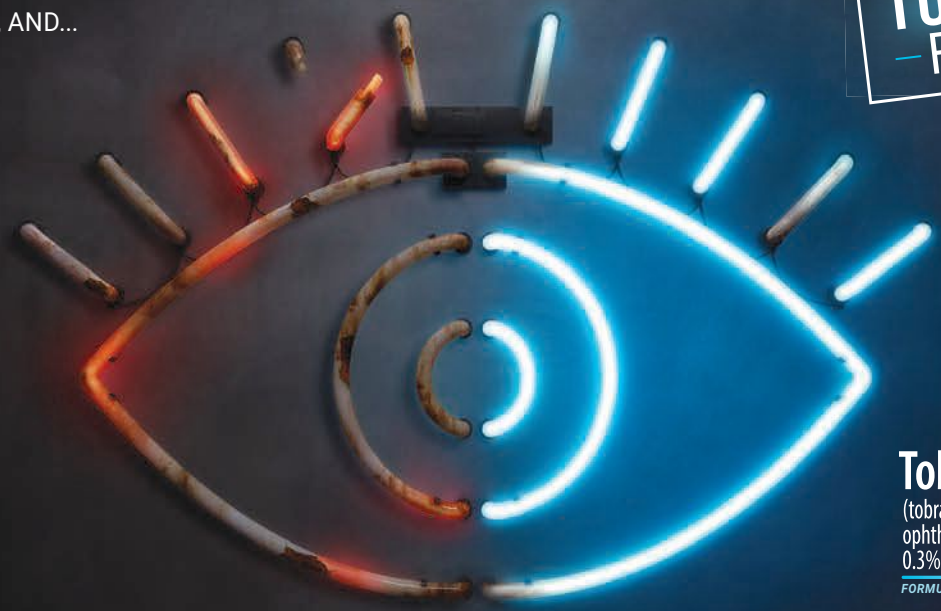
If optic neuropathy is suspected, it's recommended that the decision to discontinue the medication be discussed with that patient's prescribing cardiologist. Once the drug has been discontinued, it may take several months for the edema to resolve, ultimately leaving the patient with optic atrophy (*Figure 6*).[6]

Vigabatrin *(Sabril).* An anticonvulsant used in the treatment of seizures, vigabatrin is most often used to manage drug-resistant partial seizures and infantile spasms.

It has been associated with visual field loss and optic nerve atrophy, although the exact mechanism is unknown. These complications are typically irreversible and occur in approximately 45% of patients treated with this medication. Exam shows a bilateral, symmetric, concentric peripheral field defect with no central involvement. Retinal nerve fiber layer (RNFL) analysis with OCT shows thinning, with corresponding pallor of the optic nerves.

Even in severe case of visual field loss and optic atrophy, visual acuity can

TREAT OCULAR INFLAMMATION
AND INFECTION, AND...



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(tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%
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- XanGen™ suspension technology provides increased viscosity for improved ocular bioavailability of drug and consistent delivery[2]
- TOBRADEX ST contains half the dexamethasone as TobraDex®, yet similar ocular tissue exposure[2,b]

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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]

References: 1. Torkildsen GL, Cockrum P, Meier E, et al. *Curr Med Res Opin.* 2011;27(1):171-178. **2.** Scoper SV, Kabat AG, Owen GR, et al. *Adv Ther.* 2008;25(2):77-88.

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TOBRADEX® ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

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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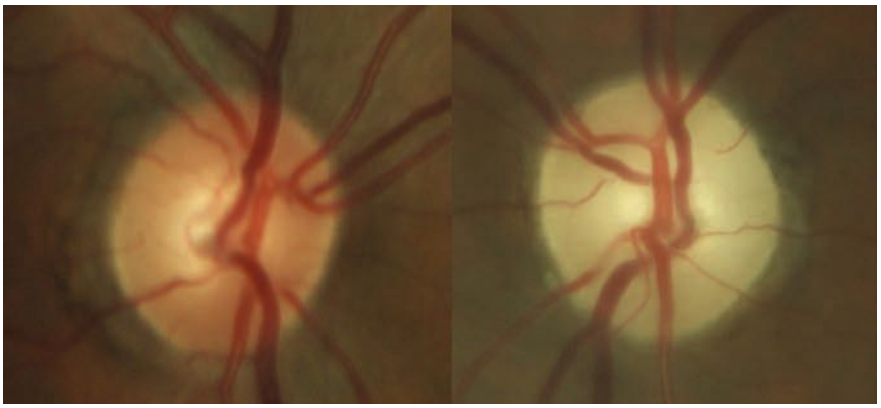
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Fig. 6. Late stage, severe optic atrophy OS in a patient on chronic amiodarone therapy.

be normal and the patient asymptomatic. The damage does appear to be dose-dependent and irreversible with the first signs of RNFL thinning showing around 1000 grams cumulative dose and worsening as that dose increases.[14]

Patients should have a comprehensive eye exam within four weeks of starting the medication, every three months during treatment and three to six months once treatment has been discontinued. If vision loss is confirmed or suspected, the prescribing physician should be consulted and the medication should be discontinued.[15]

Ethambutol *(Myambutol).* This drug treats pulmonary tuberculosis and there is significant evidence of optic neuropathy associated with its use (*Figure 7*). The condition is typically bilateral but can be asymmetric or unilateral.

The most common clinical findings include a decrease in visual acuity, color vision loss or central scotoma on visual field testing. Ethambutol may also affect the optic chiasm and cause bitemporal visual field defects. The adverse ocular effects appear to be related to dose, with those taking 60-100 mg/kg/day at the highest risk of 50%. At the recommended dose of 15mg/kg/day or less, the risk goes down to 1%.

Patients prescribed this medication should be made aware of the potential for severe, irreversible vision loss and a baseline exam, including visual field and color vision testing should be performed. RNFL OCT analysis is also recommended, as it could possibly detect early stages of toxicity. If patients are taking greater than 15mg/kg/day, it is recommended they have monthly follow-ups. Those taking lower doses may need to be followed closely if they have any conditions that may put them at higher risk for toxicity, such as diabetes, chronic renal failure or alcoholism.

The medication should be discontinued, at the discretion of the treating physician, if there is any evidence of vision loss, visual field or color vision defect.[6]

Isoniazid *(Nydrazid).* Another pulmonary tuberculosis drug, this one is commonly prescribed in combination with other meds due to concern of drug resistance to monotherapy. Isoniazid has also been associated with optic neuropathy; therefore, when used with ethambutol, it can be difficult to determine the causative agent.

Optic neuropathy from isoniazid tends to occur less frequently, is less severe and is reversible with medication discontinuation.[6] Rarely, the drug has been associated with optic neuritis. Visual symptoms are like those seen with other optic neuropathies and include decreased vision, loss of color vision and either a bitemporal or centrocecal visual field defect. The optic nerves appear hyperemic with blurred margins, though rarely may appear normal. The condition is reversible, and improvement can begin as early as four days after discontinuing the medication, with complete recovery taking anywhere from four to six months. Continuation of treatment may lead to optic atrophy.[16]

Tetracyclines. Part of a group of commonly prescribed antibiotics that also includes doxycycline, minocycline and oxytetracycline, these meds are used to treat conditions like acne, rosacea, blepharitis and dry eye syndrome.

While there is currently no evidence that they cause intracranial hypertension, they have long been associated with it. Patients with this condition most often present with headache, pulsatile tinnitus, transient visual obscurations or diplopia.

Exam findings include bilateral optic disc edema and possibly decreased visual acuity. While obese women in their childbearing years are at higher risk in general for the development of idiopathic intracranial hypertension (IIH), when associated with tetracycline use the condition tends to occur in even younger age groups (teens) and patients are less likely to be obese.

Average duration of antibiotic use before symptom onset can range from

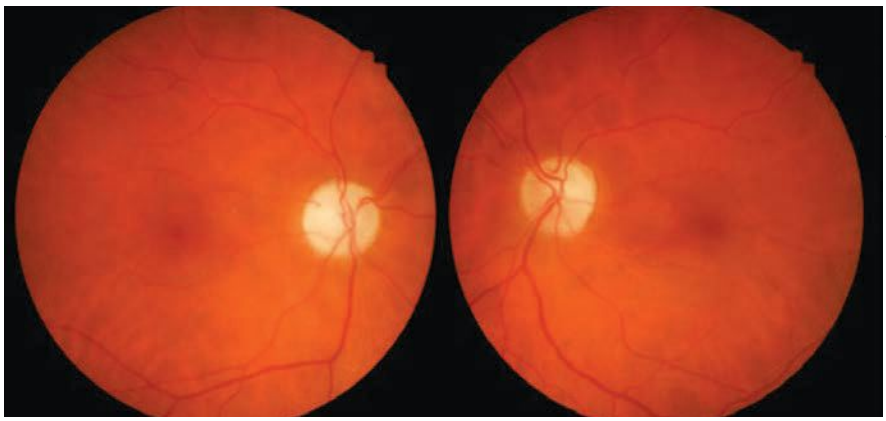
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Fig. 7. Optic neuropathy with pallor OD>OS due to ethambutol.

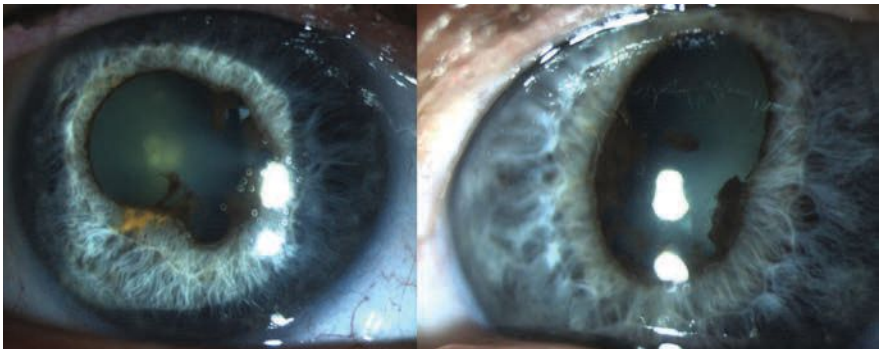
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Fig. 8. Findings due to chronic anterior uveitis associated with Keytruda use.

14.4 to 18.9 weeks.[17] IIH is a diagnosis of exclusion and additional testing, neuroimaging and cerebrospinal fluid evaluation must be performed for confirmation.[18] The condition does tend to improve with discontinuation of the medication, and recurrence—while rare—is typically less severe than the original presentation.[17]

It is recommended that patients taking tetracyclines be educated about the possible side effects and have an eye exam after one month of treatment. Patients who experience any of the common IIH symptoms should be instructed to seek prompt care with an eye care provider.[19]

Inflammatory Changes

For the remainder of our discussion, we'll shift emphasis from anatomical changes to those affecting multiple structures and/or functions, beginning with the effects of inflammation.

Alendronate (*Fosamax, Actonel, Boniva, Reclast, Prolia, Evista, Duavee).* Bisphosphonates inhibit bone resorption and are most used to treat or prevent osteoporosis in post-menopausal women.

The most common ocular side effect is uveitis or scleritis. Patients with uveitis will typically present with severe pain, redness, sensitivity to light and decreased vision. There will be cell in the anterior chamber and occasionally keratic precipitates. Scleritis will cause a severe deep pain, often that awakens the patient at night. The sclera can have a deep purple hue with vessel engorgement, and scleral edema and thinning can occur.

These conditions can be unilateral or bilateral and the onset of symptoms is two days to two weeks after starting treatment. In almost all cases of inflammation, the alendronate must be discontinued for the condition to fully resolve and reinitiating any bisphosphate prompts recurrence of the inflammation.[6,20]

Pembrolizumab (*Keytruda).* This is a cancer immunotherapy drug that works by increasing the natural immune system's ability to detect and fight cancer cells. Due to the increased immune response, this drug has been associated with ocular inflammation, specifically anterior uveitis or panuveitis (*Figure 8*).

Classic uveitis symptoms include pain, redness, photophobia and decreased vision present, typically with mild to moderate cells in the anterior chamber. It is possible, however, to have a more severe reaction with vitreous involvement. The condition is almost always bilateral and will occur within the first six months of therapy. Most patients respond well to traditional topical uveitis treatment; in rare cases, long-term inflammation and/or severe vision loss have been reported.

Patients on pembrolizumab should have a baseline exam and be educated on ocular side effects. Routine monitoring once treatment has been started is acceptable but may not be necessary unless patients become symptomatic.[21]

Mechanical Changes

Ocular effects in this category can complicate surgical procedures and, in severe presentations, expose the patient to risk of angle closure.

Topiramate *(Topamax*). An oral sulfamate originally approved as an anticonvulsant, topiramate has more recently been expanded for use for migraines, weight loss, depression and ethanol dependence.

The drug may induce uveal effusions, which result in ciliary body edema and forward rotation of the lens-iris diaphragm and angle closure glaucoma. Myopic shifts average under one diopter but have been reported at greater than eight.

Adverse events are rare, but typically occur within two weeks of starting the medication. Much rarer cases of ciliary body effusion have been reported with other sulfa drugs including acetazolamide, sulfamethoxazole, promethazine, spironolactone, isosorbide dinitrate and bromocriptine.[22] Isolated cases have also been reported with tetracyclines, bupropion, oseltamivir, duloxetine and aspirin.

Recognition of the inciting medication is critical, as the treatment differs from a primary angle closure and includes the use of cycloplegics and a topical steroid with discontinuation of the inciting medication.

Alpha-1 blockers *(Flomax, Uroxatral, Rapaflo).* These treat symptoms of benign prostatic hyperplasia (BPH).

The presence of alpha-adrenoceptors in mediating the contraction of the dilator pupillae muscle leads to a generalized miosis and the potential of intraoperative floppy iris syndrome (IFIS). This condition shows a billowing iris, rapid progressive intraoperative miosis and protrusion of iris tissue through surgical incisions. The effect tends to occur in as little as two weeks after initiation of therapy and remains even when discontinued. Severe IFIS occurs in roughly one-third of those taking Flomax and Rapaflo, while the effect is less pronounced with Uroxatral.[23]

Although the challenges surrounding IFIS cannot be eliminated with discontinuation of the drug, the intraoperative risks can be mitigated with intracameral epinephrine, preoperative atropine, intraoperative trypan blue

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The PVA program is also an opportunity for participants to build new relationships with other ECPs, says Dr. Elin Wu: "About a year ago, I visited Alcon Experience Academy in Fort Worth, Texas. It was a fun weekend of networking, learning, and discussing how to streamline soft multifocal fits through their workshop and seminars. I met a lot of wonderful talented and smart ODs there. As a result of this program, the DAILIES TOTAL1® Multifocal has been one of my go-to lenses for fitting soft multifocals for presbyopes because of the ease of fitting. Hoping for more programs like these once it's safe to gather."

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Alcon's Commitment to ECP Education—The Bottom Line

These programs and others offered through the AEA reflect Alcon's ongoing commitment to providing quality education and training for ECPs. By staying up to date on the optimal use of available clinical tools, such as multifocal contact lenses, ECPs gain the knowledge and skills they need to help their patients and practices thrive.

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Table 1. Ocular Adverse Effects of Systemic Medications

	Finding/Association	Medication or Drug Class
Cornea	Vortex/whorl keratopathy	· Aminoglycosides · Amiodarone · Atovaquone · Chlorpromazine · Hydroxychloroquine · NSAIDs · Perhexiline maleate · Suramin · Tamoxifen
	Crystalline keratopathy	· Antineoplastic agents (cytarabine, emtansine, osimertinib, vandetanib) · Benoquine · Clofazimine · Gold salts · Macrolide antibiotics · Tilorone
	Pigmented keratopathy	· Phenothiazines
	Corneal Edema	· Amantadine · Antiseptics · BAK
Sclera	Scleritis	· Alendronate
Lens	Anterior subcapsular cataract	· Phenothiazines
	Posterior subcapsular cataract	· Glucocorticoids
Uvea	Intraoperative floppy iris syndrome (IFIS)	· α-1 blockers
	Mydriasis and/or cycloplegia	· SSRIs
	Uveitis	· Alendronate · Pembrolizumab
	Uveal effusion	· Topiramate · Sulfa-based medications
Retina	Retinopathy	· Interferon-α · Tamoxifen
	Intraretinal deposits	· Tamoxifen · Canthaxanthine
Macula	Macular edema	· Tamoxifen
	Toxic maculopathy	· Chloroquines · Phenothiazines · Setraline
	Pigmentary maculopathy	· Pentosan polysulfate sodium · Phenothiazines
Optic Nerve	Edema	· Tamoxifen
	Intracranial hypertension	· Tetracyclines
	NAION	· PDE5 inhibitors
	Optic neuritis	· Isoniazid
	Optic neuropathy/Atrophy	· Amiodarone · Ethambutol · Isoniazid · Vigabatrin
Functional	Abnormal dark adaptation	· Canthaxanthine
Perceptual	Color perception changes	· PDE5 inhibitors · Voriconazole · Alendronate · Digoxin
	Oculomotor dysfunction	· Phenytoin
	Palinopsia	· Clomiphene · Mirtazapine · Risperidone · Topiramate · Trazadone

and iris retractors. As such, simply recognizing the risk and appropriate preoperative planning should minimize IFIS.

Perceptual Changes

These adverse effects may be particularly troubling to patients without necessarily representing high-risk events that jeopardize eye health.

Color Changes *(multiple classes).* PDE5 inhibitors demonstrate mild cross-reactivity with PDE6 receptors in the retina. Changes in color perception are a common side effect, with a blue tint being the most common. The effect occurs in a dose-dependent manner with a 5% chance of side effects at a standard dose. Voriconazole—a common antifungal—has a similar cross reactivity and may elicit similar changes in perception.[11] Fosamax and digoxin are commonly associated with a yellow or gold color disturbance.

Palinopsia *(multiple classes).* Defined as isochromatic afterimages which last following the removal of a stimulus, palinopsia can be caused by a wide variety of medications. Razadone, clomiphene, risperidone, topiramate and mirtazapine have been associated with these manifestations.[12] The mechanism of action is unclear, but effects on posterior cortical matter are implicated.

Blurred vision/diplopia *(multiple classes).* Blurred vision and diplopia can occur with a wide variety of oral meds. The most common classes include alpha-blockers, second generation fluoroquinolones, statins, PDE5 inhibitors and bisphosphonates. The practitioner should investigate each case to rule out the more common etiologies and medications cross-referenced with known side effects.

Functional Changes

Another patient-forward category of effects, these changes are often amenable to mitigation with discontinuation of the drug.

Phenytoin *(Dilantin).* Phenytoin is a commonly prescribed antiseizure medication and has been associated with oculomotor disturbances including gaze-evoked nystagmus, downbeat nystagmus, periodic alternating nystagmus and partial or complete ophthalmoplegia. These findings can take place in the normal therapeutic range, but are much more common in overdosed/ and toxic levels. Considering the oculomotor findings could suggest a structural brainstem lesion rather than a drug-induced side effect, it is important to review all medications to determine if a full neurologic work-up, including neuroimaging, is indicated. The clinical findings do improve and resolve once the dose is decreased or the drug is discontinued.[24]

Selective serotonin reuptake inhibitors *(Prozac, Zoloft, Paxil, Lexapro, Celexa).* SSRIs are psychiatric medications used to treat anxiety disorders.

These drugs are known to cause changes to the accommodative status due to their anticholinergic effects. They cause both mydriasis by stimulating the alpha receptors

located on the radial dilator muscle of the iris, and cycloplegia due to the paretic effect on the ciliary muscle. Patients experiencing these effects will likely complain of blur—mostly at near—and occasionally glare. Eye care providers should consider prescribing appropriate spectacle correction to alleviate symptoms. The conditions are reversible once the medication is discontinued.[25]

Keep a Watchful Eye

As we're reminded all the time in clinical practice, the eyes are not an island and are very susceptible to medication-induced side effects. Being aware of these possible effects can help providers educate their patients, quickly recognize and mitigate unwanted side effects, and avoid costly and time-consuming workups. ■

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Evolving Refraction Capabilities

By H. Jay Wisnicki, MD

Even before COVID was an issue, our New York City-based eye care practice of optometrists and ophthalmologists had been doing an increasing amount of virtual work. This has been the case for many of us in eyecare; we have been outsourcing our billing operations, front desk services, human resources, and a variety of administrative and clerical functions for many years.

At the same time, the introduction of electronic medical records (EMRs) has increased the level of medical device integration and the exchange of clinical information across the spectrum of eyecare. For example, image management software has made it possible for us to view fundus and OCT images, in addition to findings from corneal topography, biometry, ultrasound, and other digital devices between our offices and networks.

In the clinical realm, while medical specialties such as radiology, pathology and behavioral health have been conducting some form of telemedicine for years, other areas of medicine such as optometry and ophthalmology requiring a close-up view of the patient, have had a slower time making the same leap. A few areas of eyecare have successfully used telemedicine to some degree to monitor patients with, or at risk of retinal pathologies such as diabetic retinopathy or age-related macular degeneration. However, eyecare in general has not utilized remote capabilities to perform portions of the comprehensive eye examination or conduct diagnostic evaluations and tests.

That is all changing with the introduction of new software technology enabling clinicians to perform remote diagnostics, refractions and eye examinations without being physically in front of the patient.

Advancing Refraction Capabilities

There has been an evolution of refraction technology over the years, from conventional subjective refraction to computerized or digital phoropters and now remote operation.

In December 2020, Topcon Healthcare (Tokyo, Japan) introduced Topcon RDx®, an ocular telehealth platform enabling eye care providers to remotely connect to their offices to conduct portions of the comprehensive eye exam. RDx integrates with Topcon's CV-5000S digital phoropter so practitioners can virtually perform refractions, view supplementary diagnostic information through Topcon's Harmony data management software, and video consult with the patient in real time.

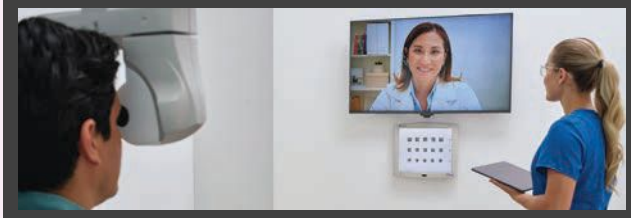
This new capability offers the patient and provider more exam flexibility, efficiency and an increased level of safety. The doctor and patient are able to virtually meet for the patient's eye exam, which helps to ensure the patient is presented with timely, high quality eye care while reducing the number of people and touch points encountered during an exam. Imagine how much more comfortable the patient might feel in a room with just one technician, while the person performing the exam is in a different location.

From a practice standpoint, this technology has transformed our busy urban clinics. Our remote optometrists are able to quickly move from patient to patient, serving patients in both of our office locations from essentially anywhere.

H. Jay Wisnicki, MD, is a professor of ophthalmology at the Icahn School of Medicine at Mount Sinai, and founder and medical director of Union Square Eye Care, all in New York City.

Topcon RDx® and the CV-5000S Digital Phoropter Benefits the Patient and the Practice

Topcon RDx®, an ocular telehealth platform enables eye care providers to connect to their offices remotely and conduct portions of the comprehensive eye exam. Topcon's CV-5000S automated phoropter integrates with RDx remotely, so practitioners can perform refractions from anywhere.



Benefits of Remote Refraction

By Ryan Ngo, OD

As an optometrist who has spent years manually and digitally refracting patients, heading into a virtual realm has required a slightly different approach to the way I practice; however, the remote refraction process is not that different from using the CV-5000S digital phoropter in the office. The main difference is that rather than using a manual control panel in the examination room, the clinician is instead using a computer interface and mouse at a remote location to control the phoropter head.

I like that the Topcon RDx platform is intuitive and easy to start using. A technician is still needed to set up and align the patient before the refraction starts, but once the program is up and running, the sequence of steps is the same as an in-person refraction. The more we use the technology, the more seamless and integrated it's becoming in our day-to-day clinical examinations.

Patient & Provider Benefits of RDx Technology

In practice, we have found that the patients' early experience with this new way of refracting has been overwhelmingly positive. After a recent remote refraction on a patient, the young woman gave us her impression of the process: "I was told prior to my exam that I would be getting a remote refraction from a clinician that would be offsite. This new examination process was so easy and was as if the doctor was still in the room with me!"

She liked the efficiency that remote refraction offered, noting: "It's nice just to be able to walk in, have a seat, video connect with the doctor and start the refraction process. I really liked that I didn't have to wait. Sometimes in busy practices the doctors are running behind schedule, but with the remote refraction, I was able to get in front of the video screen with Dr. Ngo right away and he quickly refracted me and provided a new prescription."

This patient also appreciated the additional flexibility and convenience that remote refraction offered. She said, "You have more choices now based on your schedule or what doctor you prefer to see, because the doctor does not have to physically be in the office to see you. For people who are super busy and have fast-paced lifestyles, I think the convenience and time savings with remote refraction is going to be a big value moving forward."

As an eye care provider, I also value flexibility in my professional life. Remote eye exams and refractions are especially helpful if I am travelling, unable to make it into one of our offices or need to work from home. In the past, one of the main drawbacks of being an eyecare professional was that you couldn't provide care to patients and work from home at the same time. Now that we have the ability to remotely conduct eye exams, including refractions, that opens up options for doctors who may mix in-person and remote work, switching between the two to suit their personal needs and allowing a better quality of life.

Utilization Today

In addition to its potential use for many of our routine evaluations, I think remote refraction can help improve access to vision care and fill in service gaps for large and small practices. For example, a patient who has an urgent need for glasses but can't schedule a live visit with a doctor nearby, could schedule an appointment at a practice offering remote refractions, and quickly obtain a prescription through this virtual service. In addition, high-volume specialty practices that don't do refractions might consider adding remote capabilities to offer a more comprehensive eye exam for their patients. Another application could be for small optical shops that can't afford a full-time optometrist but could hire someone part-time to manage remote refractions.

While remote refraction is an excellent fit for many patients, certain patients might not be ideal candidates. Those individuals could include patients with large degrees of astigmatism, or those who have conditions such as keratoconus or more complicated pathologies that require in-person or follow-up evaluations. Young children or elderly patients may not be as well-suited for remote refraction.

I estimate that 60% to 70% of my patient population might enjoy utilizing this new technology, in particular, "computer-age" patients like Millennials, Generations X and Z who have a comfort level with innovation and virtual technology. In all cases, it will be exciting to see where remote refraction will take eye care now and into the future.

Ryan Ngo, OD, is an optometrist at Denny Eye & Laser Center in San Francisco; he formerly practiced at Union Square Eye Care in New York City.

USING ANTIBIOTICS IN ANTERIOR SEGMENT CARE

Bacterial ocular and periocular infections are common in adults and children, but choosing an effective treatment strategy relies on more than an accurate clinical diagnosis.

BY JESSICA STEEN, OD
FORT LAUDERDALE, FL

Ocular and periocular infections present in a variety of locations from a variety of causes. The appropriate treatment course varies from observation to non-pharmacologic measures to the prescription of topical or oral anti-infective agents.[1-3] In the absence of the need for a bacterial culture, which is generally reserved for vision-threatening conditions, a careful history and thorough examination guides the clinician to determine the most likely underlying cause that can inform treatment.

To muddy the waters further, narrowing down the diagnosis to suspecting a bacterial etiology leaves the clinician with a broad range of treatment strategies. Known patterns of resistance, allergy history and systemic history complicate the choice between antibiotics in clinical practice. While treatment failure may be caused by inaccurate diagnosis, the cause may also be inadequate dosing, organism resistance, development of toxicity or allergy or nonadherence.

The chosen route of treatment typically depends on the tissue involved: soft tissue infections such as preseptal cellulitis and dacyrocystitis require antimicrobial drug levels at the site of infection, which typically requires oral administration. Conjunctival and corneal disease is most commonly treated efficiently with topical agents, while externally pointed hordeola may respond well to topical ointments and hot compresses.[1-3]

The Dangers of Overtreatment

While most anti-infective agents used in periocular infection management are considered to be broad-spectrum, emerging trends in pathogen resistance have resulted in the need for understanding most common underlying pathogens likely to cause infection and their susceptibility to commonly prescribed antibiotics. However, overtreatment through unnecessary prescribing as well as undertreatment of antibiotics persists.

Up to 80% of uncomplicated acute conjunctivitis in adults are viral in nature. In those where bacterial infection is the underlying cause, cases are typically self-limiting within seven days. Considering their self-limiting nature, topical antibiotics may not be prescribed; however, they modestly improve (by approximately two days) the time to resolution compared with supportive therapy alone.[1] Interestingly, nearly 60% of patients with acute conjunctivitis in the United States fill prescriptions for topical antibiotics.[4]

The gap between the number of cases of conjunctivitis that may benefit from topical antibiotic therapy and the number of prescriptions filled highlights the concern of over-prescribing antibiotics when not clinically indicated, a driver of antibiotic resistance.

The concept of a pre-determined set course of antibiotic therapy as a broad prescribing strategy aims to ensure complete eradication of disease-causing bacteria.[5] But a one-size-fits-all treatment approach ignores a central component to patient care: the patient. The fear of undertreatment has led prescribers to generally prescribe the same duration of treatment regardless of the patient's response to therapy.[5]

If our goal of appropriate antibiotic prescribing is centered on limiting antibiotic use based on necessity and minimizing side effects to reach clini-

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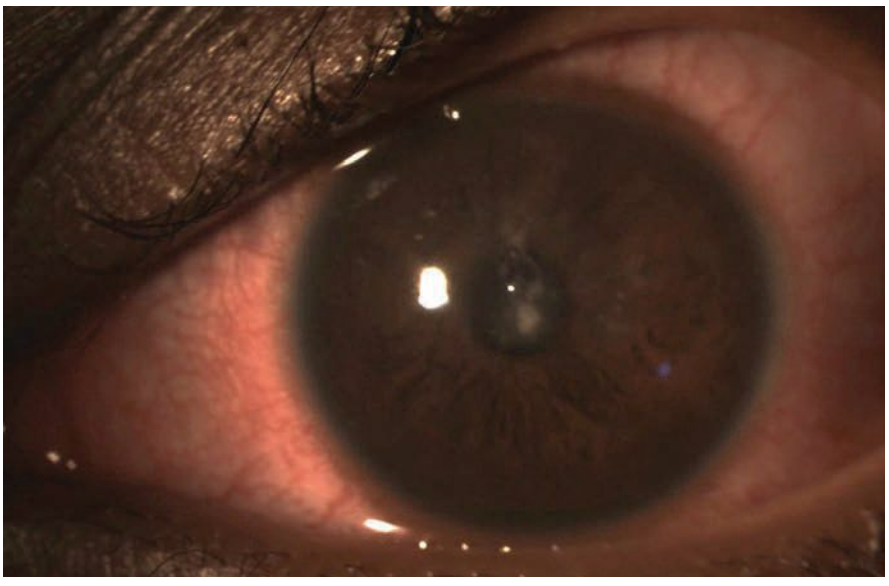
cal efficacy, antibiotic therapy discontinuation should differ based on the patient's response and how follow-up care goes. One should only continue treatment with topical ocular antibiotics for the prophylaxis of infection—for example, in cases of corneal abrasion, while the increased risk is present—while epithelial damage exists rather than for a pre-determined course.

The minimum inhibitory concentration (MIC) value describes the *in vitro* susceptibility or resistance levels of bacteria to an antibiotic and serves as the basis for assessing whether an antibiotic may be effective in a clinical setting. Undertreatment of an infection can cause failure to reach the MIC, resulting in bacteria survival, mutation and replication during treatment, increasing the likelihood of development of a drug-resistant population.[6] Never taper antibiotic agents below their equivalent MIC, which is often clinically represented by FDA-approved dosing. In order to taper a steroid in a topical antibiotic and steroid combination, first switch the patient to a steroid agent alone, rather than taper the combination agent.

A Better Understanding

The main source of bacteria causing periorbital soft tissue infection or conjunctivitis in adults is the natural flora of the eyelids and conjunctiva. Common pathogens include gram-positive cocci, such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and streptococcus species as well as *Proteus miribalis*, *Serratia marcenas* and gram-negative *Pseudomonas* species.[2,3,7,8] In children, *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most common ocular isolates in conjunctivitis cases.[8,9]

A basic understanding of the trends of resistance of common ocular isolates forms the basis for antibiotic selection for treatment with topical ocular antibiotics and oral medications to treat periocular infections. The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study surveyed antibiotic resistance patterns of common ocular isolates.[8] Its 10-year results showed that while there was no significant increase in the rates of resistance during the study period, there was generally increased resistance with age.[8] A significant proportion of *S. aureus* isolates were resistant to oxacillin/methicillin (MRSA) and at least three classes of antibiotics, termed to be "multi-drug resistant." Many believe resistance and susceptibility patterns to closely mirror patterns in systemic infections, so we can apply these findings to treatment of ocular infections with systemic and topical antibiotics.[8]



Bacterial keratitis in a soft contact lens wearer.

The study also found that more than half of all *S. aureus* isolates were resistant to azithromycin, and 33.3% were resistant to ciprofloxacin. MRSA isolates were nearly all resistant to azithromycin. Importantly, MRSA isolates were determined to be highly susceptible to trimethoprim and tetracycline, but a high percentage of isolates displayed resistance to fluoroquinolones other than besifloxacin.[8] *S. pneumoniae* isolates were most likely to be resistant to azithromycin (36.3%) and penicillin (32.2%). *P. aureginosa* isolates displayed the lowest MIC with ciprofloxacin.[8]

In general, azithromycin shows widespread resistance to the common ocular isolates implicated in ocular and periocular disease, including MRSA, which is likely a result of the widespread use of the medication. Specific resistance strategies of macrolides may be compounded by the medication's long half-life and make azithromycin a non-preferred choice for the treatment of soft tissue infections or bacterial conjunctivitis.[8,10]

Pertinent to infections in children, nearly all *H. influenzae* isolates were susceptible to all antibiotics evaluated including ofloxacin, ciprofloxacin, moxifloxacin, azithromycin and tetracycline.[8]

The ARMOR trial also determined resistance to besifloxacin to be negligible. Besifloxacin has no systemic formulation, and due to its mechanism of action, the development of resistance requires mutation in both DNA gyrase and DNA topoisomerase IV.[8] While community-acquired rates of MRSA have increased over time, individuals in healthcare settings, those recently released from the hospital, incarcerated patients and patients with a history of MRSA carry a greater possibility of harboring MRSA and therefore developing a bacterial infection due to MRSA.[3] Based on the ARMOR data on treating bacterial infections in patients who may be at increased risk of MRSA, a topical agent containing trimethoprim, such as trimethoprim sulfate and polymyxin B

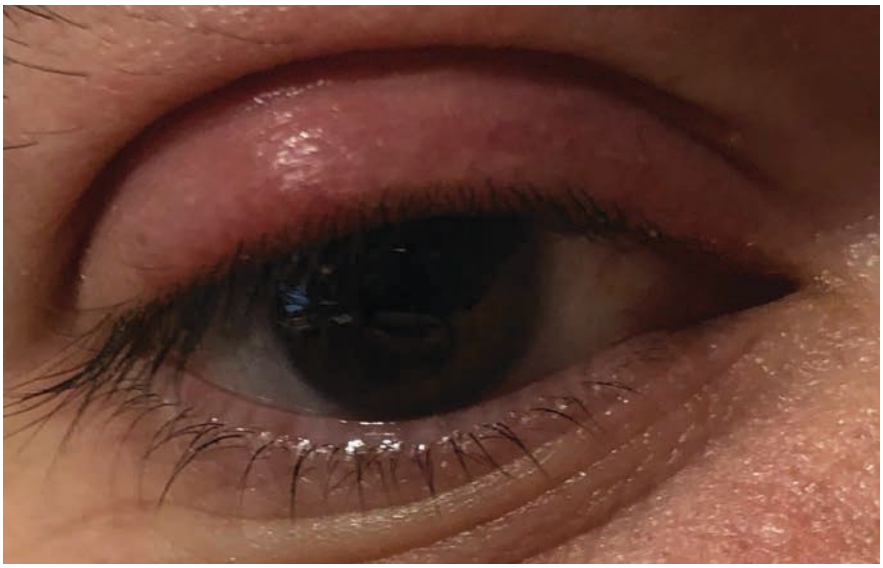


Photo: Greg Caldwell, OD

This internally pointed hordeolum of the upper eyelid may respond well to topical ointments and hot compresses.

sulfate or besifloxacin, is preferred.[8] For the treatment of infections requiring oral medication, consider trimethoprim 160mg and sulfamethaxazole 800mg, or for sulfonamide allergic patients, doxycycline 100mg.

For the treatment of bacterial conjunctivitis in children, where the gram-negative bacteria *H. influenzae* is a common underlying cause, consider fluoroquinolones such as ciprofloxacin 0.3%, moxifloxacin 0.5% and ofloxacin 0.3% ophthalmic solution. The safety and efficacy of these medications have been evaluated in children one year of age and older.[11-13]

For children younger than one year old, researchers have evaluated polymyxin B sulfate and trimethoprim sulfate in children as young as two months. While trimethoprim is not effective against *H. influenzae*, polymyxin B can provide coverage against this specific organism.[14]

Pregnancy Considerations

Every prescribing decision is based on a careful understanding and discussion with the patient of the risks, benefits and expected result of treatment. The lack of data regarding prescription medication safety in pregnant individuals stems from protections implemented to limit the study of pregnant individuals, which resulted in the difficulty of inclusion of pregnant individuals in clinical trials. This resulting lack of data may make both the prescriber and the patient reluctant to treat the underlying condition.[15]

Taking medications during pregnancy or during lactation is common, with an estimated 90% of individuals taking an over-the-counter or prescription medication during pregnancy, which means that 5.4 million pregnancies are exposed to medications annually.[16] When treating pregnant individuals, make note of alcohol use, drug use and smoking as well as inappropriately prescribed medications. Consider the risks and benefits of therapy for the patient and fetus.[17]

In general, penicillins and cephalosporins are safe to use during pregnancy.[18] Of the macrolides, azithromycin is generally safe to use, while one should use erythromycin and clarithromycin with caution and only when the benefit of treatment outweighs the risk.[18] Tetracyclines have proven teratogenicity in humans, and fluoroquinolones have concerns of fetal malformation in animals and therefore should be avoided. Avoid trimethoprim and sulfamethoxazole in the first trimester of pregnancy and after 32 weeks of gestation.[18] While systemic absorption with concurrent punctal occlusion of any topical ophthalmic agent is low, many consider topical ophthalmic antibiotic agents to be safe for use in pregnant individuals. Still, take additional clinical risk-benefit consideration for topical ophthalmic fluoroquinolones due to the risk that systemically applied agents pose.

Adverse Effects Review

When discussing the risks, benefits and expected effects of a prescribed oral antibiotic with patients, do devote a part of the conversation to likely and possible side effects. Due to orally administered antibiotics' disruption of disease-causing flora and natural gastrointestinal flora, antibiotic-associated diarrhea is common and can be expected in approximately 30% of individuals—one of the most common reasons for nonadherence to antibiotic treatment.[19]

Probiotics are ingested microorganisms, including *Lactobacillus*, *Bifidobacterium* and others, that may help to maintain or restore the natural gastrointestinal flora and ecosystem during and after antibiotic treatment; however, not all patients will respond favorably, with a determined number of 13 individual species that need to be treated in order to improve one case of antibiotic-associated diarrhea.[20]

While reconstitution of the natural gut flora is often slow following antibiotic treatment, probiotics may further delay the reconstitution to a natural gastrointestinal microbiome. Notably, gastrointestinal flora is unique to individuals. By ingesting a large amount of specific probiotic organisms, which are often not an exact reflection of the composition of an individuals's flora, the introduced species may dominate and delay recolonization of natural flora by up to five months, compared with individuals who did not use probiotics.[21]

While warnings about taking antibiotics with alcohol are often added to prescription bottles, the evidence for reduced efficacy for most antibiotics is lacking. Erythromycin, which may be prescribed in the context of periocular

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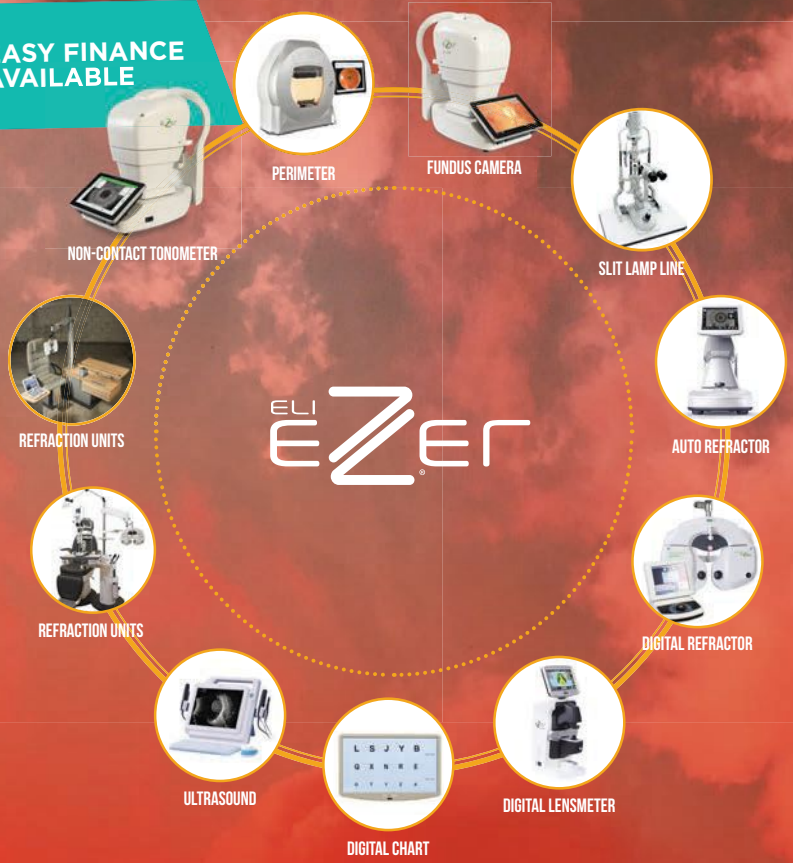

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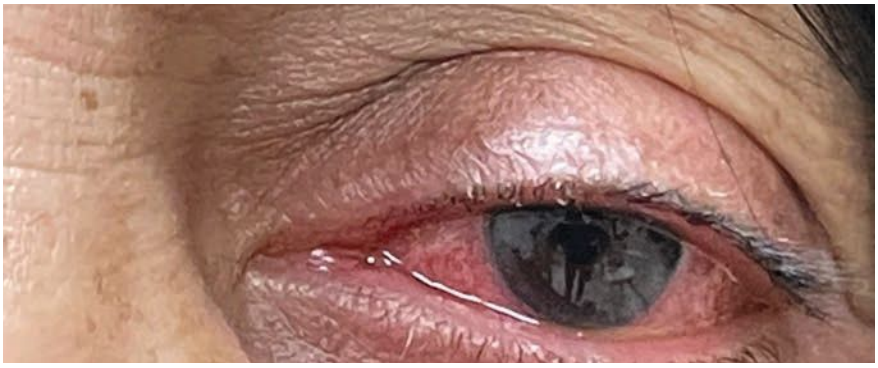
disease treatment, should not be taken with alcohol due to the potential for reduced efficacy and potential systemic toxicity.[22]

Also, cephalosporins and sulfonamide antibiotics carry a specific adverse effect that patients should be advised of. A "disulfiram-like" reaction describes specific symptoms that mimic the effect of disulfiram, a medication used for the treatment of alcohol dependency disorder. Patients may experience dizziness, sweating, headache, nausea, weakness, vomiting and hypotension—symptoms often described to be similar to the exacerbated effects of a hangover. While disulfiram-like reactions are well-documented with cephalosporin and alcohol use, only isolated case reports have been described following the administration of trimethoprim-sulfamethaxazole.[23,24]

While azithromycin is a commonly prescribed oral antibiotic, recent reports note an increased risk of sudden cardiac death due to prolongation of the QT interval in individuals with cardiovascular event risk factors that later prompted the FDA to include a black box warning for the drug.[25] Individuals most at risk are those with underlying arrhythmia termed *torsades de pointes*.[25]

Allergy Perils

Prior to prescribing any medication, perform a careful review of history of adverse drug reactions and allergies.



Hypersensitivity reaction of the left eye secondary to topical brimonidine use. Differentiating between a true type-1 hypersensitivity reaction or an IgE-mediated response and another type of adverse effect requires a careful discussion of symptoms the patient experienced with each reported adverse event.

Differentiating between a true type-1 hypersensitivity reaction or an IgE-mediated response and another type of adverse effect requires a careful discussion of symptoms the patient experienced with each reported adverse event.

Urticaria, anaphylaxis, bronchospasm, laryngospasm and angioedema are all signs of true allergy, while gastrointestinal upset is a sign of an expected adverse effect of orally administered antibiotics.[26,27] While approximately 10% of the population have reported an allergy to penicillin, less than 5% have a true allergy.[26] The allergic potential of sulfonamide antibiotics carries a similar risk, with approximately 3% of the population having experienced a true allergic reaction.[28]

The practice of avoiding cephalosporins in penicillin-allergic patients stems from the potential for cross-reactivity due to their structurally similar R1 side-chain of first- (*i.e.*, cephalexin) and second-generation cephalosporins. The risk of allergy to a cephalosporin in a penicillin-allergic patient due to cross-reactivity is much less than the historically understood 10%.[29] However, avoid cephalexin in patients with known penicillin hypersensitivity due to the approximate 1% cross-reactivity with first-generation cephalosporins.[29]

When patients have a true allergy to one type of drug—for instance, to a sulfonamide non-antibiotic such as a thiazide diuretic—is there potential for allergy to a structurally similar drug class, such as a sulfonamide antibiotic? While the potential exists for allergic reaction in both classes, it appears to not be due to structural similarity and development of cross-reactivity but rather increased propensity to allergic reaction in general.

Pay particular attention to patients with an atopic history or pre-existing asthma diagnosis, especially when they have a history of penicillin or sulfonamide antibiotic allergy. Either of these can suggest that multiple allergies may exist across non-structurally similar drug categories.[27]

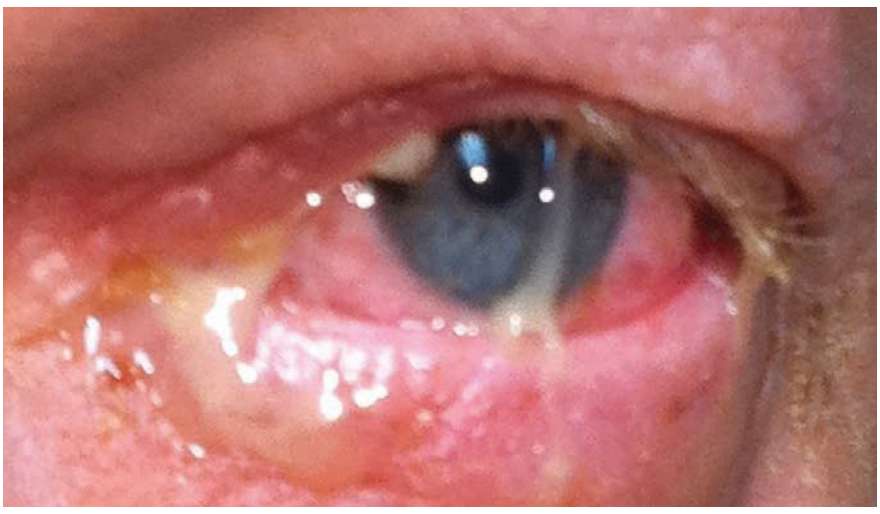


Photo: Greg Caldwell, OD

Mucopurulent discharge characteristic of bacterial conjunctivitis.

Takeaways

Optimal prescribing for the treatment of bacterial infections requires careful clinical examination, a thorough

history and an understanding of the microbiome of periocular tissues, resistance and susceptibility patterns and risk of potential adverse effects. Using the right antibiotic at the right time, dose and duration will ensure that your patient is appropriately managed while minimizing the risk of adverse effect to your patient and the greater community. ■

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MANAGING MIOTICS AND MYDRIATICS

Take a closer look at old, new and future uses of these drugs.

BY PAYMAUN ASNAASHARI, OD
SACRAMENTO

Optometrists are well-acquainted with the two opposing muscles in the iris, the sphincter and the dilator, as we witness their effects daily in clinical practice. Pupil constriction (miosis) can either be stimulated by contraction of the iris sphincter or by relaxation of the iris dilator. On the other hand, pupil dilation (mydriasis) can either be stimulated by contraction of the iris dilator or by relaxation of the iris sphincter.

Miotic and mydriatic drops work by acting on these different muscles of the iris. The drops are able to control pupil size by targeting two parts of the autonomic nervous system: the sympathetic and parasympathetic systems. Let's review their function and clinical role to better understand their present uses and why some of these agents are undergoing re-evaulation for potential new ones.

Behind the Scenes

The sympathetic pathway, mainly responsible for pupil mydriasis, involves a three-neuron pathway.[1,2] The first neuron begins in the hypothalamus and descends through the midbrain to synapse onto a specific area of the spinal cord, known as the ciliospinal center of Budge. This synapse is located between the C8 and T2 vertebrae. The second neuron, which is the preganglionic neuron, exits the spinal cord, ascends through the thorax and synapses near the apex of the lung into the superior cervical ganglion. The third postganglionic neuron travels to the cavernous sinus and enters the orbit through the short and long ciliary nerves, synapsing to the iris dilator.[1,2]

Contrarily, the parasympathetic pathway is mainly responsible for pupil miosis.[1,3] Pupil constriction starts when light enters the retina and activates the retinal ganglion cells—the beginning of the afferent arm—which then transmit their impulses into the optic nerve. This stimulus travels to the optic chiasm, through the optic tract and eventually reaches the pretectal nucleus. The impulses from the pretectal nucleus begin the efferent arm, which projects to the Edinger-Westphal nucleus. The Edinger-Westphal nucleus gives rise to preganglionic fibers, which then synapse with postganglionic neurons in the ciliary ganglion. Postganglionic neurons leave the ciliary ganglion to innervate the iris sphincter.[1,3]

Mydriatic drops work by either inhibiting the parasympathetic pathway to the iris sphincter or by promoting the sympathetic pathway to the iris dilator. Drops that antagonize the parasympathetic pathway block acetylcholine, a neurotransmitter of the autonomic nervous system, from reaching muscarinic receptors, which are located within the iris sphincter.[1,4] This leads to relaxation of the iris sphincter and promotes mydriasis.

On the other hand, mydriatic drops that promote the sympathetic pathway prevent the reuptake of norepinephrine, another neurotransmitter of the autonomic nervous system, from the synapse.[1] This allows more norepinephrine to bind to alpha-one adrenergic receptors on the iris dilator, stimulating the activation of the iris dilator and leading to mydriasis.

Miotic drops work by either promoting the parasympathetic pathway to the iris sphincter or by inhibiting the sympathetic pathway to the iris dilator.[1,5] Taking the former route, these drops mimic the activity of

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Tropicamide has a strong mydriatic effect.

acetylcholine, and when they bind to muscarinic receptors, the iris sphincter contracts and pupil size decreases.

Drops that inhibit the sympathetic pathway can also stimulate pupil miosis. These drops selectively bind to alpha-two adrenergic receptors, which are responsible for decreasing the sympathetic tone. These receptors are located on the iris dilator, which when activated leads to a decrease in the amount of norepinephrine released into the synapse. This reduces the sympathetic tone on the iris dilator and encourages pupil miosis.

Miotic Drops

These drops can be used for a number of things, including diagnosis of pupil abnormalities (*e.g.*, Adie's tonic pupil) and treatment of ocular hypertension, acute angle closure, dry eye and post-surgical glare.[3] Exercise caution or avoid use altogether in patients who are pregnant, breastfeeding or at risk of retinal detachment. The following are several established drops and associated clinical pearls of each:

Parasympathomimetics. Pilocarpine is a miotic drop that is used primarily to treat ocular hypertension.[6] It can effectively lower intraocular pressure (IOP) and is easily accessible. However, it can also induce myopic shifts and precipitate retinal detachments. For these reasons, pilocarpine is not commonly used in general practice.

Pilocarpine is a direct muscarinic acetylcholine agonist, or a parasympathomimetic. It binds to the M3 muscarinic receptor, an excitatory receptor in the iris sphincter and ciliary body. This leads to an upregulation of calcium and smooth muscle contraction of the iris sphincter and ciliary body. The contraction of the iris sphincter causes the pupil to decrease in size, and the contraction of the ciliary body opens the trabecular meshwork, decreasing IOP by enhancing aqueous outflow.

Sympathomimetics. Brimonidine and apraclonidine are miotic drops that are typically used to lower IOP and assist with post-surgical glare, ocular redness and diagnosis of pupil abnormalities (*e.g.*, Horner's syndrome).[7] These drops are able to rapidly lower IOP and are readily available. They are contraindicated in patients with underlying asthma and those taking MAO inhibitors. They are also more strongly associated with allergic reactions.

Both of these drops exhibit selective alpha-two adrenergic agonist activity. They bind directly to alpha-two adrenergic receptors, which are inhibitory receptors of the sympathetic system. These receptors are present on the iris dilator, ciliary body and conjunctival blood vessels. They cause a downregulation of cAMP and a decrease in the sympathetic tone, leading to iris dilator relaxation, increasing uveoscleral outflow and decreasing aqueous production and vasoconstriction.

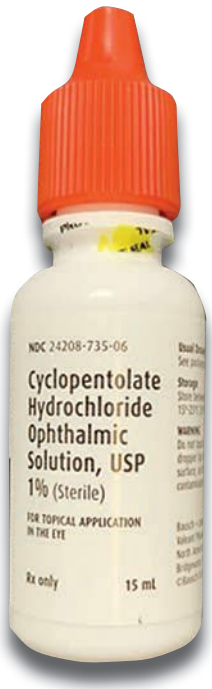
Mydriatic Drops

These drops can be used to perform dilated fundus examination, diagnose pupil abnormalities (*e.g.*, Horner's syndrome), treat anterior uveitis and engage in pharmacological penalization for amblyopia.[2] Exercise caution or completely avoid use in patients who are pregnant or breastfeeding and in those who have anatomically narrow angles. The following are several established drops and associated clinical pearls of each:

Parasympatholytics. Tropicamide, cyclopentolate and atropine are all mydriatic drops that are traditionally used for dilated fundus examination, paralysis of accommodation, anterior uveitis treatment, myopia control and pharmacological penalization for amblyopia treatment.[8-10]

Tropicamide is typically used for dilated fundus exam, paralysis of accommodation and anterior uveitis treatment. It has a strong mydriatic effect, rapid onset and shorter duration of action in comparison with cyclopentolate and atropine. Its disadvantages include its ineffectiveness at inhibiting accommodation and its side effects of light sensitivity and blurred vision.

Cyclopentolate is commonly used to inhibit accommodation and treat amblyopia and anterior uveitis. It is effective at accommodation paralysis. On the other hand, it has a long onset of action, long duration of action and



Cyclopentolate can effectively inhibit accommodation to help treat amblyopia and anterior uveitis.

Phenylephrine should not be the sole drop used for dilated fundus examination, as it has a weaker mydriatic effect.

side effect profile that includes light sensitivity and blurred vision. The long duration of action makes this a viable drop of choice for anterior uveitis treatment to prevent anterior synechiae.

Similar to cyclopentolate, atropine is traditionally used to inhibit accommodation, manage amblyopia, treat anterior uveitis and provide myopia control. It has a strong mydriatic effect and is effective at inhibiting accommodation and slowing the progression of myopia. Its disadvantages mirror those of cyclopentolate.

The mechanism of action of each of these drops is identical: they all have direct antimuscarinic activity. They competitively bind to muscarinic receptors on the iris sphincter and ciliary body and inhibit their activity. This results in a downregulation of calcium and induces smooth muscle relaxation of the iris sphincter and ciliary body.

Sympathomimetics. Phenylephrine is a mydriatic drop that is traditionally used for dilated fundus examination, ocular redness relief and diagnosis of pupil abnormalities (*e.g.*, Horner's syndrome).[11] It has a rapid onset of action and is easily accessible. However, it has a weak mydriatic effect and should not be used alone for dilated fundus examination.

Phenylephrine promotes the sympathetic pathway as a selective alpha-one adrenergic receptor agonist. Alpha-one receptors are excitatory receptors of the sympathetic system and reside in the iris dilator and conjunctival blood vessels. Activation of these receptors causes an upregulation of cAMP, which leads to iris dilator contraction and vasoconstriction.

Sympathomimetics and parasympatholytics. Paremyd (hydroxyamphetamine 1% and tropicamide 0.25%, Akorn) is a mydriatic that is traditionally used for dilated fundus examination.[12] It has a rapid onset of action, reduced effect on accommodation and shorter duration of action. Its disadvantages include a reduced mydriatic effect on dark irides, decreased ability to inhibit accommodation and a side effect profile that includes light sensitivity and blurred vision.

Hydroxyamphetamine acts as an adrenergic agonist and blocks the breakdown of norepinephrine. This increases the sympathetic tone and indirectly initiates contraction of the iris dilator. Tropicamide has antimuscarinic activity and inhibits the muscarinic receptors on the iris sphincter, leading to pupil dilation.

In the Pipeline

The exploration of pharmaceutical advancements in the areas of myopia control, presbyopia and dilation is on the rise.

Myopia. The increasing prevalence of myopia worldwide and its associated risk factors have led to a public health crisis. Historically, orthokeratology has been a leading option for slowing myopic progression, but ophthalmic drops are catching up and may potentially surpass this modality. Treatment with low-dose atropine has been increasing in popularity as more evidence continues to show its effectiveness. The Atropine for the Treatment of Myopia studies (ATOM 1 and ATOM 2) demonstrated the effectiveness of low-dose atropine. The investigators found that if the concentration of atropine is low enough, it is possible to avoid side effects of photophobia and blurred vision while still controlling myopic progression.[13,14] The Low-Concentration Atropine for Myopia Progression (LAMP) study showed that 0.05% atropine had the most profound effect on minimizing myopic progression and axial elongation compared with 0.01% and 0.025%.[15]

Furthermore, new clinical studies are looking into the effectiveness of combination treatments for myopia control. The Bifocal and Atropine in Myopia (BAM) study is assessing the pharmacological effect of 0.01% atropine with the optical effect of soft bifocal contact lenses.[16] Studies like these could lead to additional novel strategies to either optimize or provide greater slowing of myopia progression than single-treatment strategies.

Presbyopia. Another area of focus for pharmaceutical companies has been developing noninvasive treatments for presbyopia. The race to develop effective treatments for the underlying cause of symptoms is underway.

One of the most interesting avenues of presbyopia treatment involves the use of topical drops to alter the pupil size to aid near vision. The challenge with miotic drops is avoiding too much pupil constriction, as this can have a negative impact on distance vision, night vision and even visual field. The key to a productive presbyopia drop is finding the miosis "sweet spot."

Allergan is in the process of developing a presbyopic drop known as AGN-190584, which consists of an optimized formulation of pilocarpine, a muscarinic receptor agonist, the activation of which causes the iris sphincter and ciliary body to contract. This can enhance depth of focus and promote accommodation.[17]

Another company, Orasis, is also developing a miotic drop to constrict the pupil, known as CSF-1. Its complete composition has not yet been released, but it appears to be a combination of

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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 adjacent page.

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CEQUA™ (cyclosporine ophthalmic solution) 0.09%
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INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

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

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.

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SUN OPHTHALMICS

a parasympathomimetic agent and a nonsteroidal anti-inflammatory agent in an oil-based vehicle.[18]

In addition, Presbyopia Therapies is developing a presbyopic drop, called Liquid Vision, that produces miosis without stimulating accommodation. Rather than using pilocarpine, the active ingredient is aceclidine, which has a different mechanism of action that may provide a greater depth of field than pilocarpine.[19]

Visus Therapeutics is using a combination of ingredients to achieve a similar effect. Brimochol is a once-daily drop that combines carbachol and brimonidine tartrate to provide functional near vision for at least eight hours.[20]

While recent pharmaceutical strategies for presbyopia focus on altering pupil size and the ciliary body, others are investigating targeted approaches to alter the crystalline lens. Studies have suggested that the formation of disulfide bonds within the crystalline lens restricts the ability of the lens to change shape in response to ciliary muscle contraction.[21] Due to its decline in flexibility with age, altering the lens shape could be a future avenue for novel treatment strategies.

Routine dilation. Newer mydriatic drops for routine dilation did not exist until recently. Eyenovia is nearing FDA approval for its new drop, MydCombi, which contains a fixed combination of phenylephrine and tropicamide. The drop would be the first microdosed ocular therapeutic that contains a smart delivery system. According to the company, Eyenovia's Optejet dispenser is designed to provide a consistent, efficient and easy touchless application of two mydriatic medications. The bottle design of MydCombi contains no protruding parts, which can help prevent accidental interaction with the ocular surface.[22]

Reverse dilation. Currently, there are no FDA-approved drops to reverse pharmacological dilation. Ocuphire Pharma is currently developing an option that counteracts the side effects of routine pupil dilation. The drop, Nyxol (phentolamine 0.75%), is currently undergoing clinical trials to determine its safety and efficacy.

With a drop like this, subjects may be able to return to near baseline pupil diameter and accommodation within two hours, independent of the mydriatic agent used. Patients commonly defer routine dilation due to the long-lasting and disruptive side effects. If Nyxol shows promise, it could offer a novel solution to significantly improve the patient experience when it comes to routine dilation.[23]

Take-home Message

The autonomic nervous system plays an important role in managing pupil size. Parasympathetic and sympathetic innervation compete for control over the pupil. The sympathetic system dilates it, while the parasympathetic system constricts it. The diameter of the pupil at any time reflects the balance of these two forces acting simultaneously.

The pupil response to miotic and mydriatic drops is directly dependent on which of these two autonomic systems is activated or inhibited. These drops continue to play a pivotal role in clinical practice, with new alternatives paving the way for treatments that were previously unavailable. ■

Paremyd is commonly the drop of choice for pupil dilation.

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MAKE GLAUCOMA THERAPY MORE PATIENT-FRIENDLY

Here's how to better ensure patient adherence to treatment.

BY MICHAEL DORKOWSKI, OD, SHALEEN RAGHA, OD, AND JENNIFER SANDERSON, OD
MEMPHIS

It is estimated that glaucoma affects over three million Americans and over 76 million adults over the age of 40 worldwide.[1,2] By 2050, glaucoma is expected to impact nearly eight million adults in the United States and over 110 million around the globe.[3] Glaucoma is a leading cause of blindness, and the only proven therapy that has been shown to decrease the risk of progression is reducing intraocular pressure (IOP).[4,5]

Historically, topical medications were the mainstay therapy; now the most effective management involves a continuum of both medical and surgical treatments.[6,7] Multiple factors determine which treatment paradigm bests suits each patient. Details such as the disease severity at the time of diagnosis, rate of disease progression, age of the patient, ocular and systemic comorbidities, allergies, previous therapy, cost of treatment, target IOP and other patient-specific issues and preferences must be considered.[8]

Helping patients understand the disease, set long-term expectations, embrace various therapeutic options and anticipate potential hurdles plays an essential role in successful outcomes; namely, slowing the progression of the disease and reducing vision loss. This article focuses on the specific factors optometrists should address with their patients for the best results with topical therapy.

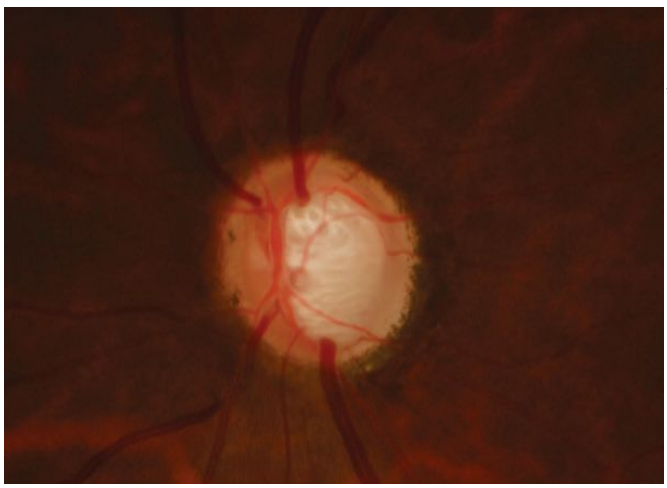

Photo: The Eye Center at SCO

Glaucomatous optic nerve.

Price and Acquisition

Cost is one of the most important things to keep in mind to encourage adherence to therapy and patient compliance.[9,10] Financial constraints are a real issue many patients face in today's healthcare system. Data from the National Center for Health Statistics indicates roughly 10% of the US population was uninsured in the first quarter of 2020.[11] With the COVID-19 pandemic, these statistics are expected to worsen as loss of jobs means loss of employer-provided insurance.[12] Even having insurance or a Medicare plan does not necessarily guarantee an associated drug benefit. Sampling a new drop is only effective if the patient can afford it, let alone locate it at a nearby pharmacy and tolerate its side effects.

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Lifetime medication use is expensive, especially if the disease progresses and the patient requires additional therapy. This factor must be weighed against surgical intervention and the associated set of fees and adverse effects. After taking all costs into consideration, one study found that selective laser trabeculoplasty (SLT) is typically less expensive than most long-term brand name medications.[13] Another study reported that SLT effectively maintained IOP in newly diagnosed glaucoma and ocular hypertensive patients over a 36-month period.[14] Patients who had SLT were at or below target IOP readings for more follow-ups than their counterparts on topical therapy.[14]

Prescribing generic medications when possible can also be a less costly alternative. However, the cost of generic medications is set by each individual pharmacy, so price may vary widely, even within the same community. Two optometrists started werx.org to help patients determine the cost analysis of medications across local pharmacies for both name brand and generic medications. A similar feature is offered on www.goodrx.com. Many pharmacies and other organizations (including ScriptSave WellRx) have membership plans that offer opportunities for reduced medication cost. It would be beneficial for prescribers to review local providers to evaluate what ophthalmic drugs may be available and at what cost.

Additional web-based resources such as www.needymeds.org and www.blinkhealth.com offer ways to assist patients in navigating the cost of their medications, including one-stop access to manufacturer-sponsored patient assistance programs, coupons, rebate programs and even drug delivery. Discussing all of these options with patients can help them understand their choices and how to best afford their care.[15]

To that end, online formulary search tools can ensure the recommended therapy is cost effective for each patient. Many insurance providers post their medication formularies online through easily accessible platforms. There are also several search engines and associated cell phone apps that offer information on medication coverage for a multitude of insurance providers in a region. Such resources include www.formularylookup.com, lookup.decisionresourcesgroup.com, www.epocrates.com and www.healthcare.gov.[16]

Insurance considerations and financial concerns can be a limiting factor to medication compliance, yet optometrists spend little time discussing the cost of therapy with their patients—a barrier that we can easily overcome.[17,18] Even if the patient is able to afford and obtain the prescribed medication, non-adherence is one of the most important and costly worldwide healthcare problems.[19] A recent study demonstrated that roughly half of patients who start topical glaucoma therapy are noncomplaint or have completely discontinued their prescribed medications by six months.[20] An additional study analyzed dispensing records to determine the degree of adherence for glaucoma medication refills at community pharmacies and found that over a 12-month period, only about 57% of patients had the proper amount of medication to last the year.[19] In addition to cost and accessibility, several other factors can help us avoid these outcomes.

Table 1. Combination Medications Commercially Available in the United States

Name (Manufacturer)	Ingredients
CoSopt/CoSopt PF (Akorn)	timolol maleate 0.5% + dorzolamide hydrochloride 2%
Combigan (Allergan)	timolol maleate 0.5% + brimonidine tartate 0.2%
Simbrinza (Novartis)	brinzolamide 1% + brimonidine tartate 0.2%
Rocklatan (Aerie)	netarsudil 0.02% + latanoprost 0.005%

Routine and Regimen

Patients often have difficulty fitting glaucoma drops into their established routine due to forgetfulness.[21-23] Asking patients about the details of their daily routine, such as when they wake up, work, eat and sleep, can assist in drop integration. When a patient's lifestyle needs dictate an atypical dosing schedule, optometrists must understand how to best accommodate the patient. For example, patients who have evening or overnight work schedules may benefit from altering the typical nightly dosing regimen and instead take prostaglandin analogs in the morning in conjunction with their sleep schedule to maintain IOP. One study showed that mean 24-hour IOP control was equivalent when comparing travoprost dosed in the morning vs. in the evening.[24]

If a patient is already compliant with other regimens such as oral medications and self-care routines such as brushing teeth, placing the eye drops near their medication or toothbrush may improve compliance with therapy. To optimize the 12- or 24-hour effect of the bulk of glaucoma drops,

Table 2. Compounded Combination Medications Available Through ImprimisRx

brimonidine (0.15%) + dorzolamide (2%)
timolol (0.5%) + brimonidine (0.15%) + dorzolamide (2%) + latanoprost (0.005%)
timolol (0.5%) + brimonidine (0.15%) + dorzolamide (2%)
timolol (0.5%) + dorzolamide (2%) + latanoprost (0.005%)
timolol (0.5%) + latanoprost (0.005%)

The Autodrop Eye Drop Guide (Maddak) can help patients with drop instillation.

setting reminders can be beneficial. Cell phone alarms, calendar alerts and app reminders are all options. A study showed that 72.9% of glaucoma patients expressed interest in using an app, one of the more popular routes that we can take advantage of.[25] Along with these recommendations, pharmacy auto-refills or mail orders are also advised so that patients do not run out of their medications.

The complexity of the dosing regimen can also affect adherence. Simply adding a second eye drop to the regimen can increase dosing errors by nearly 400%.[15,26] There are a multitude of combination agents available commercially and through compounding pharmacies that can make treatment coordination and adherence easier for patients (*Tables 1 and 2*).[27]

Adherence to follow-up appointments is still necessary to complete diagnostic testing to ensure the patient's daily routine and glaucoma medication are sufficient in disease control, and pre-appointing follow-up exams helps ensure patients return for their ongoing assessments.

Instillation

Administering the drop itself can be exceedingly difficult for some patients with limited mobility or arthritis. Poor aim, inability to extend their neck and dexterity issues can all add up to cause an undesirable result. In fact, one study found that nearly nine out of every 10 glaucoma patients were unable to instill eye drops correctly.[28] Another found that patients administer an average of seven drops before they feel confident in the instillation process.[29] The author of the latter study published a video titled "Glaucoma Drop Operator Error" that can be found at eyetube.net/videos/glaucoma-drop-operator-error.

Finally, other researchers concluded that despite excellent confidence in their ability, patients rarely administer topical ophthalmic drops without touching the bottle to their eye, which increases risk of infection.[30] Punctal occlusion or eyelid closure for three to five minutes post-instillation is an important final step of the process that many patients miss, as it can have the intended effect of increasing ocular penetrance and decreasing systemic absorption.[31]

In-office training, including watching the patient administer a drop to their eye, can help mitigate and correct many instillation mistakes. To aid in the instillation process, there are several different types of auto drop mechanisms and guides on the market.[32] Some are pharmaceutical company-specific, and others can be obtained online for use with a variety of different-sized bottles. One study proposed using an alternate instillation technique into the medial canthal area over a closed eyelid.[33] The investigators observed similar reductions in IOP with this method compared with direct instillation onto the cornea.[33] Directing your patient to resources on drop administration such as www.glaucoma.org and www.aoa.org can be beneficial in giving them a reference point and tips on how to apply the medication to the eye.[34,35]

Complications

Side effects of medications are another common barrier to drug adherence encountered by patients with glaucoma. These patients overcome the obstacles of obtaining and instilling the drop only to be thwarted by intolerable adverse events, which can be temporary or persistent. Stinging, redness and burning are common sequelae of drop instillation. Storing the drop in the refrigerator can help alleviate these complaints and helps the patient with proper administration onto the ocular surface as the drop is easier to detect.[34]

Another consideration is the effect these medications have on pre-existing ocular conditions or diseases, especially when it comes to dry eye.[36] Controlling and treating the underlying disease concurrently with glaucoma treatment can help prevent ocular discomfort. Preservatives that are inherent in topical therapy can exacerbate discomfort, specifically benzalkonium chloride (BAK).[37] To alleviate this dilemma, use of preservative-free medication—Zioptan (tafluprost, Akorn), CoSopt PF (dorzolamide hydrochloride-timolol maleate, Akorn), Timoptic in Ocudose (timolol maleate, Bausch + Lomb)—or alternatives to BAK-preserved medication—Travatan Z (travoprost, Novartis), Alphagan P (brimonidine, Allergan), Xelpros (latanoprost, Sun Pharmaceutical)—are recommended, especially for those who require additional therapy.[38]

Requesting the patient bring their medication bottle with them to subsequent appointments may be necessary when attempting to decipher patient

When it comes to ocular surface inflammation, FLAREX® is A PROVEN WINNER

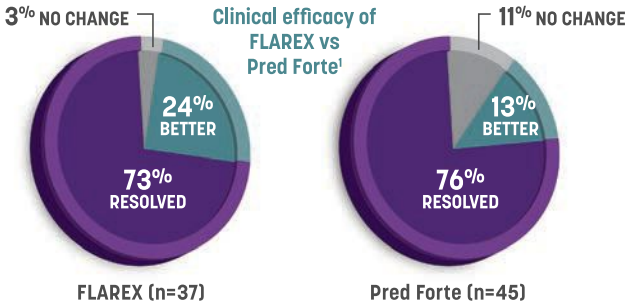
The power of Pred Forte* (prednisolone acetate ophthalmic suspension, USP) 1% with the safety of FML* (fluorometholone ophthalmic suspension, USP) 0.1%[1a]

Ocular surface inflammation is a key etiological factor in Dry Eye Disease[2]

FLAREX offers the efficacy of Pred Forte for ocular surface inflammation[1]

In the FDA pivotal trial evaluating patients with ocular surface inflammation,[a] there was no significant difference in clinical efficacy with FLAREX vs Pred Forte, *P*=0.49.[1]

97% of ocular surface inflammation was resolved or improved with FLAREX vs 89% with Pred Forte[1]



FLAREX is a steroid ester and the *only* acetate derivative of fluorometholone.[3-5] The acetate group improves lipophilicity, allowing greater penetration across the cell membrane.[6]

In clinical trials, there were no adverse reactions reported in the FLAREX and FML treatment groups and FLAREX and Pred Forte treatment groups.[1]

There is no generic equivalent of FLAREX—be sure to prescribe by name[4]

INDICATIONS AND USAGE
FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.
IMPORTANT SAFETY INFORMATION
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.

[a]**STUDY DESIGN:** The efficacy and safety of FLAREX were evaluated in two identical, randomized, double-blind clinical trials. In one trial of 78 patients with ocular surface inflammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes, patients administered either FLAREX (n=41) or fluorometholone alcohol (n=37) every 2 hours for the first 2 days and then every 4 hours thereafter, with signs and symptoms of inflammation assessed at Days 1, 3, 8, and 13. In a separate but identical trial in 82 patients with ocular surface inflammation, patients administered either FLAREX (n=37) or prednisolone acetate 1.0% (n=45). At each visit, investigators determined if signs and symptoms in the involved eye were resolved, improved, unchanged, or worsened. If a patient was rated as signs and symptoms resolved before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.[1]

Flarex®
(fluorometholone acetate ophthalmic suspension) 0.1%

FLAREX NDC NUMBER: 71776-100-05

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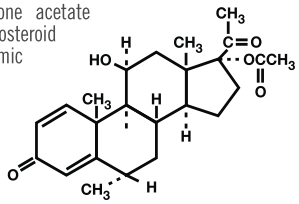
When it comes to ocular surface inflammation, FLAREX® is

A PROVEN WINNER

DESCRIPTION: FLAREX® (fluorometholone acetate ophthalmic suspension) is a corticosteroid prepared as a sterile topical ophthalmic suspension. The active ingredient, fluorometholone acetate, is a white to creamy white powder with an empirical formula of C24H31FO5 and a molecular weight of 418.5. Its chemical name is 9-fluoro-11, 17-dihydroxy-6 -methylpregna-1, 4-diene-3, 20-dione 17-acetate. The chemical structure of Fluorometholone Acetate is presented above:



Each mL contains: Active: fluorometholone acetate 1 mg (0.1%). Preservative: benzalkonium chloride 0.01%.

Inactives: sodium chloride, monobasic sodium phosphate, edetate disodium, hydroxyethyl cellulose, tyloxapol, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. The pH of the suspension is approximately 7.3, with an osmolality of approximately 300 mOsm/kg.

CLINICAL PHARMACOLOGY: Corticosteroids suppress the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Corticosteroids cause a rise in intraocular pressure in susceptible individuals. In a small study, FLAREX (fluorometholone acetate ophthalmic suspension) demonstrated a significantly longer average time to produce a rise in intraocular pressure than did dexamethasone phosphate; however, the ultimate magnitude of the rise was equivalent for both drugs and in a small percentage of individuals a significant rise in intraocular pressure occurred within three days.

INDICATIONS AND USAGE: FLAREX (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

CONTRAINDICATIONS: Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of 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: FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION. Use in the treatment of herpes simplex infection requires great caution. Prolonged use may result in glaucoma, damage to the optic nerve, defect in visual acuity and visual field, cataract formation and/or may aid in the establishment of secondary ocular infections from pathogens due to suppression of host response. Acute purulent infections of the eye may be masked or exacerbated by presence of steroid medication. 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. It is advisable that the intraocular pressure be checked frequently.

PRECAUTIONS:

General: 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.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the suspension. The preservative in FLAREX® (fluorometholone acetate ophthalmic suspension), benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX (fluorometholone acetate ophthalmic suspension) but may be reinserted 15 minutes after instillation. Patients should be advised that their vision may be temporarily blurred following dosing with FLAREX (fluorometholone acetate ophthalmic suspension). Care should be exercised in operating machinery or driving a motor vehicle.

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

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.

Nursing Mothers: 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 (fluorometholone acetate ophthalmic suspension), 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.

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.

Postmarketing Experience: The following reaction has been identified during post-marketing use of FLAREX® (fluorometholone acetate ophthalmic suspension) 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.

DOSAGE AND ADMINISTRATION: 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.

HOW SUPPLIED: FLAREX (fluorometholone acetate ophthalmic suspension) is supplied in white low density polyethylene (LDPE) bottles, with natural LDPE dispensing plugs and pink polypropylene closures. The product is supplied as 5mL in an 8 mL bottle.
5 mL: NDC 71776-100-05

STORAGE: Store upright between 2°C -25°C (36°F -77°F). Protect from freezing.

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complaints and confirm they are taking the correct drug in the first place.

Patient Education

Upon prescribing a new medication, effective education can help guide patient expectations moving forward.[39] Patients may notice mild momentary blurring or clearing of their vision from the effect of the drop on the ocular surface and assume it is a problem with the efficacy of the medication rather than a temporary adverse effect.[21] We can resolve this popular misconception with clear communication prior to the patient beginning their regimen. If side effects persist and are intolerable, however, patients must understand the importance of calling the office, as the medication may be substituted.

Glaucoma management can be fraught with miscommunication, and health literacy plays an important role in patient compliance and disease treatment.[22] A study found that 44% of patients in an urban American setting did not have an acceptable idea of what the term "glaucoma" means and that 30% were unsure as to why they were taking medications in the first place.[40] Without appropriate understanding of their disease or its management, patients lose motivation and can progress to advanced stages of glaucoma due to poor adherence to treatment and follow-up.[41]

Many individuals may not even want to pursue treatment until symptoms present; hence, doctors must advise that the associated vision loss is irreversible. Patients should be reminded that treatment is not geared toward prevention of glaucoma, but rather prevention of vision loss. Along these lines, patients should not get into the habit of assuming a lower IOP reading equates to adequate control and stop using their drops or only use them prior to an appointment.

Patients should also be informed of their test findings and rate of progression, when applicable. Perceptual visual field loss can be vastly different from what doctors observe on automated visual field testing. One study found

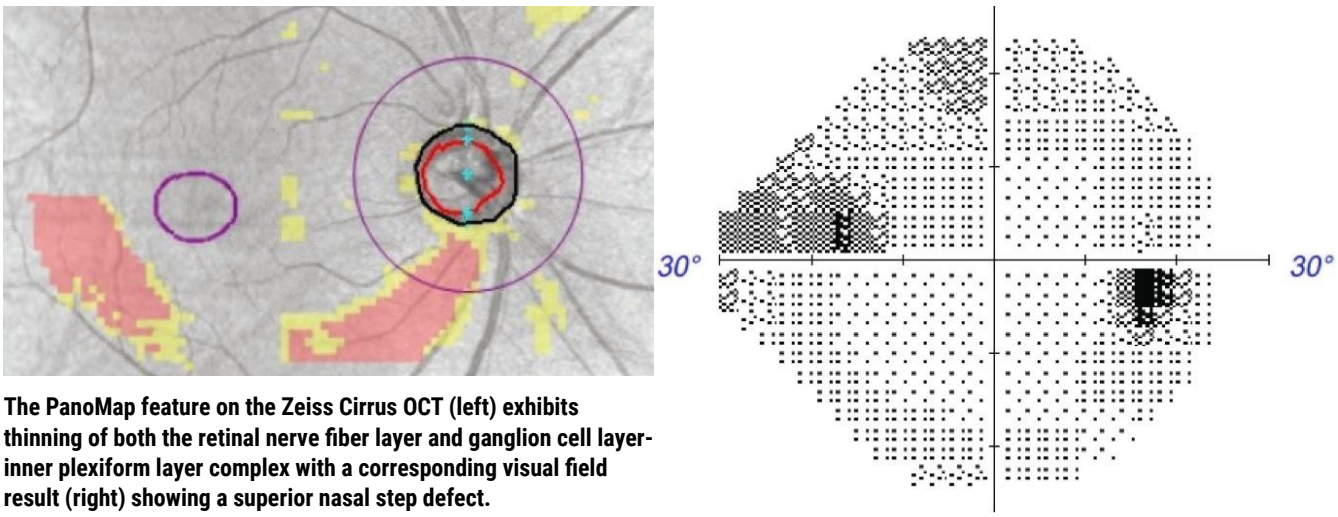
Glaucomatous visual defects tend to appear as negative scotomas, but rather than presenting as dark or blurred, the brain creates an inaccurate but believable image in the defective visual field using surrounding retinal images. By late stages of the disease, the brain no longer receives sufficient visual input to compose an image.

45% of patients were completely unaware of the true nature of their vision loss.[42] The survey showed that patients do not have tunnel vision or perceive black spots in their vision; rather, they see blurred patches. Patients should be informed that glaucoma is slowly progressive and they will likely be asymptomatic until advanced visual field loss occurs. Hence the importance of treatment continuation despite perceived subjective improvements.

Some patients rarely participate in preventive care or routine screenings or physicals to begin with. These patients may only seek medical care if any problems or symptoms that do arise fail to improve. On the other hand, some patients are too discouraged to seek out medical care, whether due to trust issues with the physician or unfavorable practice conditions.[22,43] If one optometrist discovers glaucomatous risks or signs when a previous provider did not, the patient may question their judgment. Patients may also assume their glaucoma is similar to an acquaintance's, but glaucoma status varies based on type of glaucoma, rate of progression and treatment history.

Written instructions as a follow-up to verbal education can help alleviate misunderstandings the patient may encounter. A study showed that even after a patient has been successful with their drug regimen for over a year, continued education and positive reinforcement have ongoing benefits.[44] Another confirmed positive reinforcement increases short-term improvements in measures regarding adherence.[15] As optometrists, it is our job to continuously educate our glaucoma patients on the purpose of their therapy and follow-ups, and the risks of abstinence and progressive visual loss.[23,45]

Photos: The Eye Center at SCO



The PanoMap feature on the Zeiss Cirrus OCT (left) exhibits thinning of both the retinal nerve fiber layer and ganglion cell layer-inner plexiform layer complex with a corresponding visual field result (right) showing a superior nasal step defect.

Takeaways

Glaucoma patients are in it for the long haul. Place an emphasis on clear, direct instructions to aid in manageable, patient-friendly care. Be supportive and empathetic while actively listening and providing solutions to patient concerns regarding possible barriers to effective treatment. Advocating for your patient and helping them overcome the challenges they may face will assist in ensuring a successful partnership in their long-term care. ◀

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TAKE THE FEAR OUT OF COMANAGING NEURO CASES

Many patients are best served through a partnership between primary care optometrists and appropiate subspecialists.

BY CATLIN NALLEY
CONTRIBUTING WRITER

Comanagement, a key aspect of optometric practice, can take many forms and this is especially true for neuro-ophthalmic cases. These complex conditions, which can be vision- or life-threatening, require timely collaboration across various specialties.

While challenging, these conditions can be comanaged successfully and optometrists are in the perfect position to take a leadership role in the care of this patient population.

"It's important to recognize that there are too few neuro-ophthalmologists to effectively manage the number of patients that present with neuro-ophthalmic disorders," notes Leonard Messner, OD, an optometric expert in care of neuro-ophthalmic disease and vice president for patient care services at Illinois College of Optometry. "Therefore, it is very important that the general optometrist has a fundamental knowledge and understanding of these disorders to ensure comprehensive patient care."

Recent research highlights the important role ODs can play in the management of these patients and the need for a comprehensive understanding of these conditions. A prospective, cross-sectional study of cases sent to neuro-ophthalmology subspecialists (from both optometrists and general ophthalmologists) found that the referral diagnosis was incorrect in 49% of cases.[1] The researchers reported that 26% of misdiagnosed patients suffered harm, which could have been prevented by earlier referral. In 23% of cases, patients experienced inappropriate laboratory testing, diagnostic imaging or treatment prior to referral.

Clearly, there's plenty of headroom for optometry to grow its capabilities in triaging neuro cases.

Given the seriousness of these conditions, tackling the management of neuro-ophthalmic patients can be overwhelming. As a part of our comanagement series, this article will help lay the framework for a strong referral relationship as well as offer clinical pearls and practical advice to give ODs the confidence to take on these patients.

Determining the Referral Pathway

Unlike other areas of optometry, such as cataract or cornea care, the referral pathway for neuro-ophthalmic cases is not always straightforward. Therefore, it is important for ODs to have a clear plan on when and to whom they refer.

Michael DelGiodice, OD, PhD, who practices in New Jersey, has access to neuro-ophthalmologists; however, it can still be challenging to get appointments for patients quickly. "I typically always comanage with neurology," he explains, noting that neuro-ophthalmologists usually work with neurology as well. "As optometrists, we have the knowledge and skills to work directly with these specialists."

Comfort level plays a key role in the referral pathway an optometrist chooses to follow, notes Kelly Malloy, OD, professor and chief of neuro-ophthalmic disease at Pennsylvania College of Optometry. "If an optometrist has the confidence to do so, they can directly handle imaging and referral to neurology and neurosurgery," she says. "Since timely intervention is critical for many neurologic conditions, it is important to take the most direct referral route whenever possible."

That isn't to say that neuro-ophthalmology has no role to play. For non-urgent cases, they can serve as a second opinion or additional resource, notes Dr. DelGiodice. In emergency situations, waiting for an appointment with a specialist—whether that's the neuro-ophthalmologist or neurologist—is not always an option. Those

cases require the ODs to make a judgment call and send their patient to the emergency department for immediate care. Once admitted to the hospital, the patient will then be able to more acutely benefit from the knowledge and expertise of neuro-ophthalmologists, neurologists and other specialists as needed, according to Dr. Malloy.

In some cases, the best specialist may not be neurology related. For instance, Dr. DelGiodice will refer a patient with unilateral disc edema or signs suggestive of incipient disc edema to a retina specialist for immediate, same-day fluorescein angiography (FA). "These cases obviate the need for neuro-ophthalmic referral because the FA will elucidate the seat of the pathology," he notes.

Fostering Strong Relationships

Like any comanagement relationship, building a partnership based on mutual trust and respect is vital to success. This begins by finding specialists who not only have strong clinical skills but also value the important role optometry plays. Without this, a true comanagement relationship that benefits both patients and providers is not possible.

"Effective comanagement requires a high level of coordination between providers, whether that is the neuro-ophthalmologist, neurologist or primary care provider," notes Dr. Messner. "Building and maintaining a strong relationship depends on communication."

Direct, consistent communication helps take the guesswork out of case management. "Nothing can replace picking up the phone and communicating peer-to-peer. This ensures the relationship is a two-way street and everyone is on the same page," emphasizes Dr. Messner. "That is the art and science of medicine. It is the essence of taking care of people properly."

Given the complex, and often subtle, nature of neuro-ophthalmic conditions, ODs must feel comfortable working collaboratively, but finding the right specialist can be a challenge. Visiting physicians at their office, whether by appointment or dropping off your resume and making a quick introduction, can be a good way to build connections, according to Dr. DelGiodice.

"Writing comprehensive letters is another way to enhance the referral relationship," he says, noting that this is an effective approach to showcase your own skills and knowledge of neurologic conditions. Dr. DelGiodice also suggests taking it a step further and calling the office to discuss the case as well. "Comanagement becomes easier as you build that trust and both providers are confident in one another's abilities."

Optimizing the Approach to Neuro-Ophthalmic Care

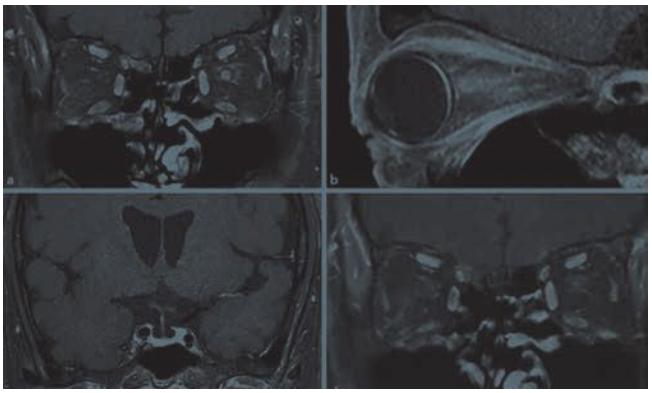
Understandably, many neuro-ophthalmic conditions can pose a challenge for optometrists. Neuro abnormalities can present within any of the three main components of the eye examination (afferent assessment, efferent assessment and ocular health assessment) and these conditions often have features that overlap with a variety of other ocular and systemic conditions. Determining when and when not to refer can be a difficult task.

Common neurologic complaints optometrists may encounter include diplopia, vision loss or visual disturbances, and headaches. Facial and lid abnormalities, such as ptosis, proptosis, facial weakness, head turn or tilt, and blepharospasm, can also indicate neurologic eye disease.[2]

As with any type of condition, a detailed history is a vital first step, followed by a comprehensive eye exam. This should include blood pressure measurement, relative afferent pupillary defect assessment, measuring pupils and eyelids, visual field testing and OCT.[3] In addition, a cursory neurologic examination can also help significantly with localization of the abnormality.

"Optometrists should always consider that every patient might have a neuro-ophthalmic disease process," suggests Dr. Malloy, who notes that while it may be obvious among patients who present urgently, ODs also need to pay attention for signs of neuro-ophthalmic disease in patients who present for routine care without any specific complaints. "It is important to comprehensively assess the afferent and efferent visual systems

Photo: Kelly Malloy, OD



The appearance of optic neuritis on MRI. Optometrists should be comfortable knowing when and why to order neuroimaging work.

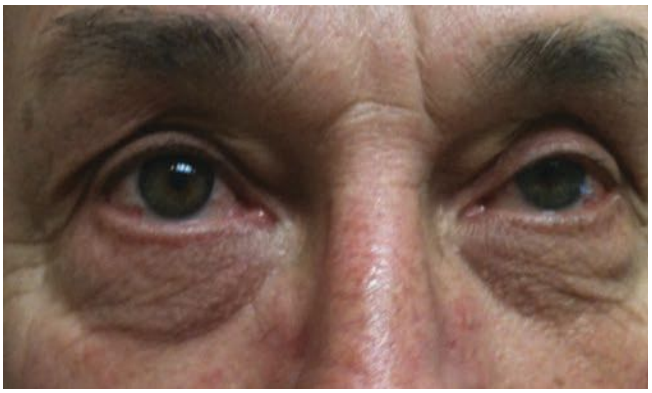


Photo: Christopher Suhr, OD

As many as 60% of myasthenia gravis patients, such as this one, present with ptosis and diplopia.

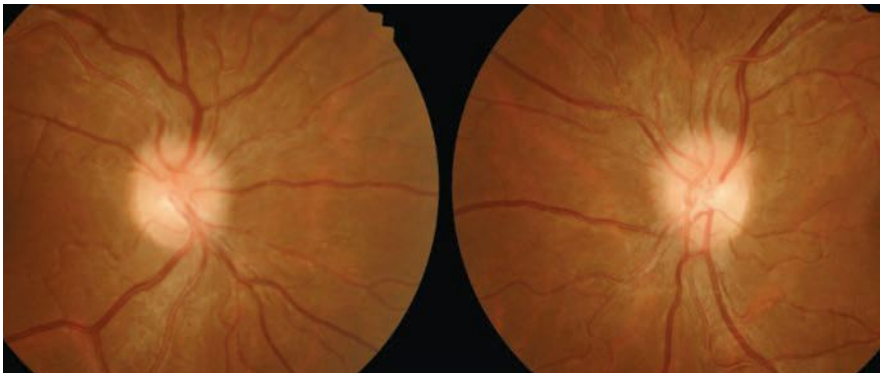


Photo: Joseph Sowka, OD

Idiopathic intracranial hypertension is fairly commonly diagnosed by optometrists—and it's incumbent on them to coordinate care, says Dr. Messner.

as well as the ocular health status of every patient."

Navigating when a referral is necessary and when it isn't depends on a fundamental understanding of these conditions as well as the necessary testing. "ODs must be able to recognize the signs and symptoms of underlying neurologic disease and conduct appropriate tests," Dr. Messner says. "And, when needed, work hand in hand with either neuro-ophthalmology or neurology for the betterment of the patient."

For example, there are number of vision and eye movement problems associated with multiple sclerosis, including optic neuritis and brainstem motility abnormalities. The general optometrist should be able to recognize these issues and work with neurology to evaluate and manage these individuals effectively.

Once patients have been diagnosed with multiple sclerosis, the OD continues to play a role in their long-term comanagement. For example, communicating follow-up OCT and visual field findings to neurology can help them determine stability and adjust treatment plans as needed.

A condition that Dr. Messner sees frequently is idiopathic intracranial hypertension. "A key finding associated with this disease is papilledema," he says. "So, these are individuals that invariably are initially seen by optometrists with comanagement by neurology."

However, this does not mean the optometrist's role ends with the referral. Someone still needs to be following the patient's vision and doing regular visual fields and OCTs, notes Dr. Messner. "Neurologists, to a large extent, do not have the fundamental knowledge of the visual field or OCT interpretation, and this is where optometry must take the lead. This is comanagement in its truest sense."

When a condition necessitates a referral, optometrists should maintain relationships with both the specialist and patient to ensure they continue to take a leadership role in care. Communication with the neurologist or other specialists is crucial throughout follow up.

"I make a point to schedule an appointment with my patient after they see the neurologist and I will continue to manage their visual challenges," explains Dr. DelGiodice. "This can include, for example, running OCTs or visual field tests. The results of all of those images and testing are then sent to the neurologist. While they are taking care of the chronic management of a patient's disease, I am following the patient and continuing to manage their visual needs."

One of the most challenging—and potentially daunting—aspects of neuro-ophthalmic comanagement is the life-threatening implications some conditions may have. Optometrists must be able to recognize when a situation is an emergency and when it is not. Conditions that require immediate referral to the emergency department include aneurysm, giant cell arteritis, acute stroke, papilledema, pituitary apoplexy and carotid artery dissection.[3]

In these cases, timing is critical; ODs need to be ready to take immediate action and send their patients to the emergency department. Referring to their primary care provider or another specialist could cost the patient valuable time. "Optometrists have a significant role to play in recognizing emergency cases and acting accordingly," explains Dr. Malloy, who suggests that ODs stay current on the latest recommendations as well as participate in ongoing continuing education to ensure they have the confidence to make these calls.

Recommendations and standards of care can change from the time an OD graduates from optometry school, notes Dr. Malloy. "More recently, we have seen this with how acute transient vision loss and symptomatic retinal emboli are managed," she says. "We now understand that these conditions should be treated the same as acute stroke, requiring the patient be sent immediately to an emergency department of a hospital with a dedicated stroke center."

Effective Patient Communication

A sometimes difficult but important aspect of comanagement is patient communication. This involves not only explaining a diagnosis or reason for referral, but helping them through the process of seeing a specialist.

CONDUCTING A COMPREHENSIVE NEURO EXAM[4]

The neurologic exam is a vital part of comanaging neuro-ophthalmic conditions and can easily be conducted in the optometry office. Key components of the exam, include:

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TABLE 1. COMMUNICATION GOALS AND TECHNIQUES FOR NEURO-OPHTHALMIC REFERRALS

	WHAT TO COMMUNICATE	HOW TO COMMUNICATE THIS INFORMATION
COMMUNICATE WITH PATIENT/FAMILY	Why referring to emergency department or specialist	• Explain reasoning to both patient and family/support system (in person or via phone) that they need more evaluation to rule out or prevent a particular problem, or to find out the etiology of their signs/symptoms. • Ask what questions they have to help them better understand the reason for referral. • Give them a way to contact you if they think of additional questions later. • Emphasize that keeping this appointment is in their best interest.
	How to prepare for the referred visit/referral	• Write out details of upcoming appointment (date, time, exact location). • Write out doctor/facility NPI number and tell the patient to call their PCP for a referral if necessary. • Write out instructions on what to bring with them to the appointment (test results, MRI disc, medications). • If they need to have outpatient testing prior to referred appointment, give them any necessary scripts and write out timeline of when testing should be done/is scheduled. • Explain what to expect at upcoming appointment or emergency department visit. • Give them an appointment card for a follow-up visit with you.
COMMUNICATE WITH PROVIDER TO WHOM YOU ARE REFERRING	Key history and/or in-office clinical findings	• Phone call preferred, especially for emergent or urgent referrals, or when sending to ED. • Comprehensive letter, including clinical findings to back up phone conversation should be faxed or sent via secure email to avoid delay. • VF, OCT and/or optic disc photos sent to highlight significant clinical findings and demonstrate interval change. • Be sure the provider has a way to reach you to further discuss he patient during the visit, if needed.
	External testing/work-up	• Phone call and/or letter indicating testing OD deems necessary for provider to perform/order. • Phone call and/or letter indicating outpatient or inpatient testing that has been previously obtained. • Send copies of all reports to provider via fax or secure email to avoid delay.
	Conditions that need to be ruled out	• Phone call and/or letter indicating conditions of concern and any noted signs or symptoms consistent with each.
	When patient should return to see the OD	• Make it clear that you plan to continue to comanage the patient, and include the date of follow-up appointment with you. • Each time the patient does see you in follow-up, communicate (via a comprehensive letter) with all of their providers to keep them updated regarding patient progress. This will prompt the other providers to regularly communicate with you as well as you continue to comanage the patient.

When discussing neurological concerns, ODs must strike a balance between conveying the seriousness of a condition without unduly alarming their patient. "You don't want to overstate the diagnosis," suggests Dr. DelGiodice, "because the majority of the time you're not going to have a definitive answer yet."

Using words like *proactive* or *preventive* while describing your recommendations and actions can be a good approach with patients. "The key is to communicate," says Dr. DelGiodice. "Explain the process and let them know that you will be following up with them after they see the specialist." When patients hear you taking the lead in coordinating their care, they tacitly acknowledge that your role in their care will continue even as other doctors become involved.

"There's a tendency to think that if you scare someone [with a dramatic description of the condition], they're actually going to follow through" and urgently see a specialist, Dr. DelGiodice continues. "However, in my experience, it has the opposite effect. Often, the patient will shut down and won't process what you are saying."

Handling emergency cases requires a nuanced approach, he notes. An emergent situation still doesn't mean you should scare your patients, but you do need to emphasize that moving quickly is in the best interest of their health and overall well-being.

Dr. DelGiodice goes the extra mile to make sure his patients have support, especially when they have to contend with a visit to the emergency department. He provides them with a note for the doctor as well as his phone number and tells them to call if they have any questions or need help.

The optometrist should also call the hospital and, if possible, speak with either the neurologist on call, emergency department doctor or at least the triage nurse to explain the patient's presentation and why it warrants emergency evaluation, suggests Dr. Malloy.

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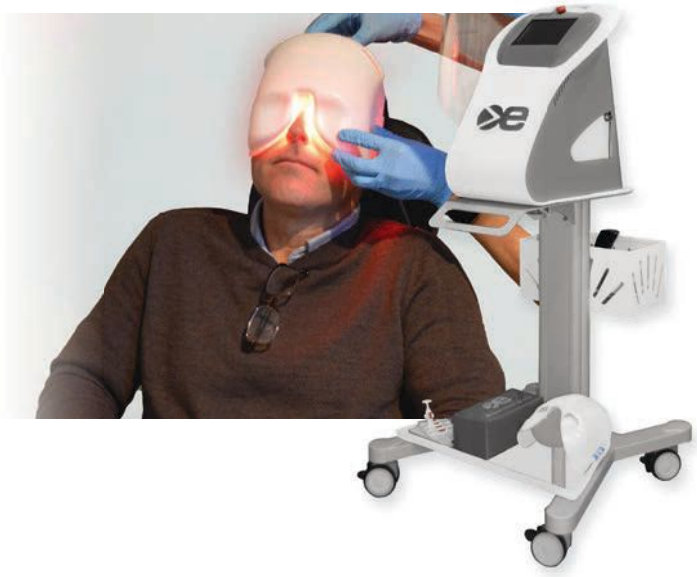

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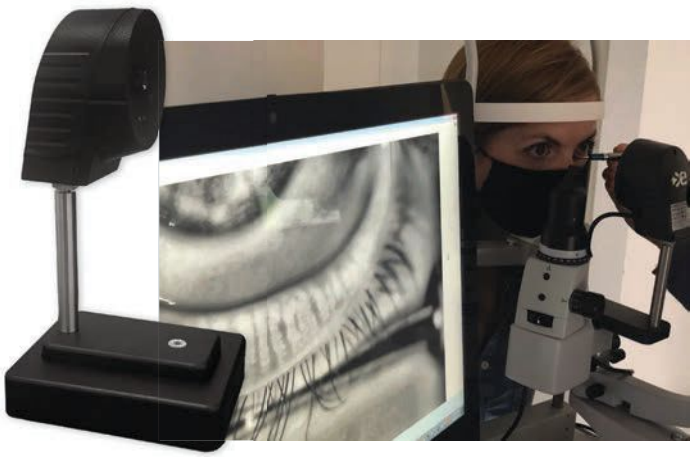

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When a patient adamantly refuses to go to the emergency room, Dr. DelGiodice will follow up with the patient as well as connect with one of their other providers. This may not be their PCP but rather the person they see most frequently, such as their cardiologist. "In these situations, sending your patient back to a provider they haven't seen in two years is not an effective approach," he notes.

Table 1, developed by Dr. Malloy, lists many specific points to communicate to patients and comanaging providers.

Ongoing Education & Growth

Given the wide range of neuro-ophthalmic conditions as well as their complex nature, continuing education and professional growth is necessary for the ongoing enhancement of your practice.

One way to build your confidence when assessing these cases is through mentorship. "Fostering a mutual relationship with someone who does neuro work, ideally a fellow optometrist, is an excellent way to grow your skills," notes Dr. DelGiodice. "This will help you become more comfortable with timing and diagnosis of these conditions."

An area where mentorship could be very useful is double vision, according to Dr. DelGiodice, who notes that given the subtlety of this issue, building up skills on your own can be very challenging. Optometrists should also continue to develop their ability to interpret visual field and OCT findings for patients with neuro-ophthalmic disorders, notes Dr. Messner, who emphasizes the importance of keeping up with the latest technologies.

"It's fascinating to see how technology is evolving, particularly in the area of OCT," he says. "We're able to look at the structure of the optic nerve and retina almost down to a cellular level. It's been said now that we really need to be looking at OCTs the same way that neuroradiology looks at the MRI and I think that is absolutely true."

Another key component related to the care and comanagement of these patients is knowing which neuroimaging studies to perform. Any OD who wants to take this aspect of their practice to the next level must devote significant time to honing these skills.

As mentioned above, optometrists should play a central role in the management of these patients, including ordering imaging. With a shortage of neuro-ophthalmologists, especially in more rural areas, ODs should be prepared to take charge of these patients. "The optometrist should be fundamentally involved in ordering neuroimaging studies, MRI and CT scans," explains Dr. Messner.

"We don't want to abrogate this responsibility to the primary care physician or the general ophthalmologist," he continues. "As optometrists, we are the ones seeing the patient and we have the greatest understanding of their clinical manifestations; therefore, it is our responsibility to take the lead."

Optometrists need to know which imaging studies correlate with which conditions. Who needs a CT? Does the patient require an MRI with or without contrast? Once you have identified the condition, ODs must feel comfortable directing the imaging center. "Proving localization and directions for the proper imaging study is crucial," says Dr. DelGiodice. "The final part, which can be more challenging, is reviewing the scans."

Over time, the OD's experience will grow, and they will become more comfortable reading the scans. Some may ask, is this a necessary step? "I think it is important because it is our field," notes Dr. DelGiodice. "If you're comanaging with a neurologist, you want to know what you are looking at. This step may be less necessary if you are working with a neuro-ophthalmologist; however, I believe improving your skills in this area will only enhance your practice."

Dr. DelGiodice makes a point to request the discs and review all of the scans. If questions arise, he will connect with the neuroradiologist. He acknowledges that not everyone has direct access to this specialty. However, the OD should always have the ability to call and speak with the reading radiologist regardless of where they work and/or where the study was performed. In addition, comanaging with neurology or neuro-ophthalmology can allow for another opinion regarding neuroimaging findings when needed.

With limited access to neuro-ophthalmologists as well as cases that often require timely intervention, it is critical that ODs be positioned as leaders in care for patients with neuro-ophthalmic conditions. Effective comanagement begins with ODs and their desire to explore what are often complex and challenging cases.

"Most patients present with subtle clinical signs, so you have to be able to carve out the time to carefully evaluate these cases and you have to be curious," concludes Dr. DelGiodice. "Curiosity is paramount when it comes to managing these conditions." ■

KEY TAKEAWAYS

- Establish strong referral pathways depending on the condition.
- Determine the urgency of the clinical presentation.
- Maintain open lines of communication with comanaging specialists.
- Take the lead on neuroimaging and patient management.
- Support patients through clear, consistent communication.
- Take advantage of CE and mentors to hone your skills.

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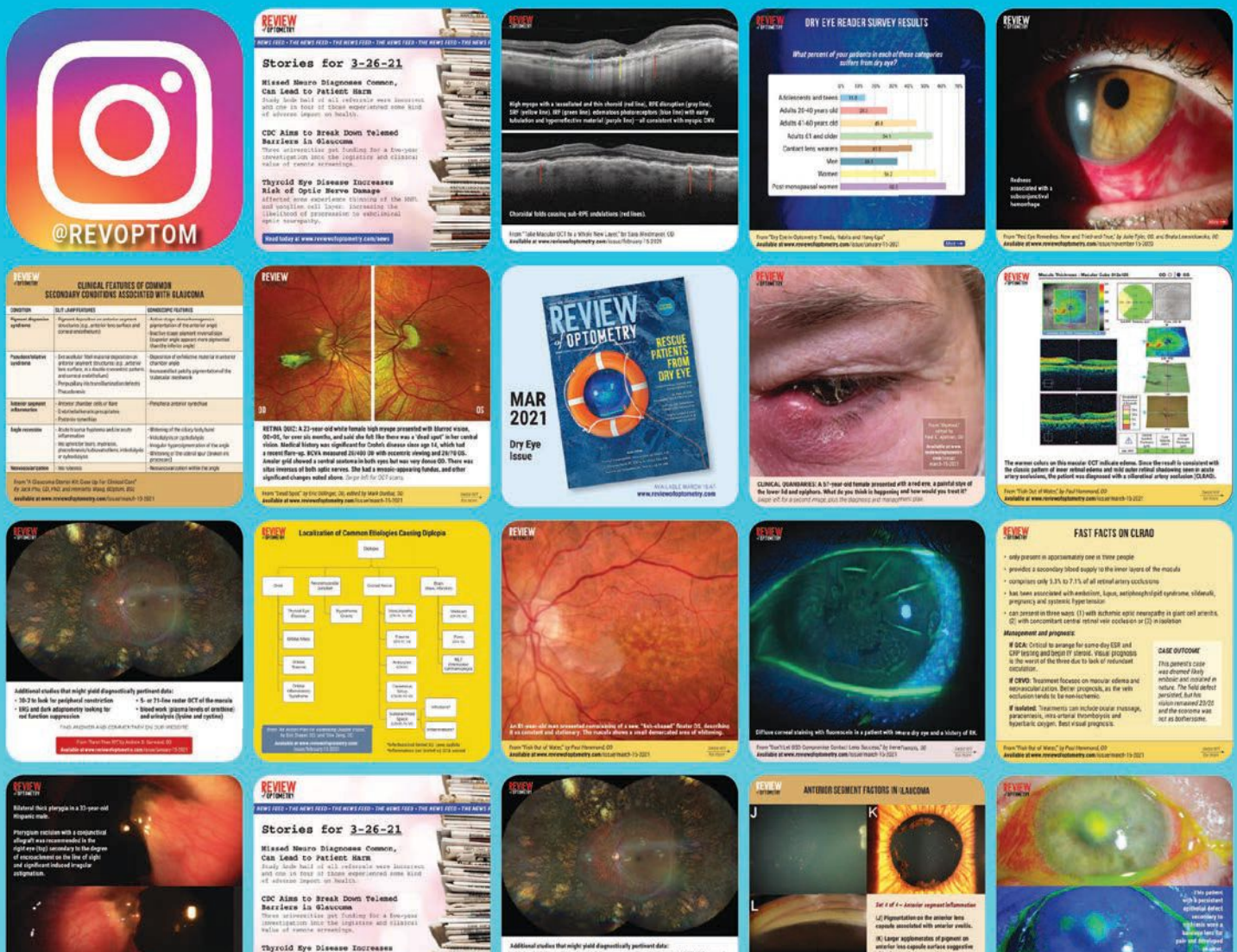

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GET TO KNOW HZO

Gain a comprehensive understanding of the various treatment options to effectively manage this condition.

BY AARON BRONNER, OD
KENNEWICK, WA

Determining the right avenue of treatment for herpes zoster ophthalmicus (HZO), which occurs when the varicella-zoster virus (VZV) is reactivated in the ophthalmic section of the trigeminal nerve, can be a challenge. While antiviral use during the acute, infectious stage is common, treatment in later, post-infectious stages can vary. With the potential for chronic and recurrent disease, it can be difficult for clinicians to identify the right management approach.

The purpose of this article is to review what we do know about HZO, including its clinical manifestations. We will also delve into its treatment and where these concepts diverge from its cousins herpes simplex virus (HSV) 1 and 2, with which HZO is sometimes mistakenly blended in our education.

Clinical Manifestations

While shingles lesions occur most commonly on the trunk and abdomen—which is where the disease gets its name—the most frequently involved cranial nerve is the trigeminal nerve (CN V). When the ophthalmic branch of the CN V is affected, the condition may affect the ocular structures, at which point it may be described as HZO, an entity accounting for 10% to 20% of all cases of zoster.[1,2]

The cornea is among the most frequently involved ocular tissues in HZO. Keratitis occurs in up to 65% of HZO cases and has varied manifestations.[3,4] In seeking to distinguish this from its cousin HSV keratitis, it's useful to point out that while HSV corneal disease may vacillate from one manifestation to the next without any particular chronology, HZO seems to follow a sequential chronology with some manifestations possible in the first few days and weeks after the initial infection and others only manifesting months to years following the episode.[1,5]

Infectious epithelial keratitis. As with HSV, true infection of the corneal epithelium sets the stage for other corneal manifestations, and with VZV this initial infection begins as focal patches of coarse vesicular epithelial keratitis. There are often multiple lesions scattered across the cornea. Within one to three days' time, these lesions either regress or coalesce to form pseudodendrites.[1,5] Despite similar names and gross appearance, pseudodendrites, which appear in 50% to 75% of cases of HZO corneal disease, are readily distinguished from the HSV dendritic equivalents primarily though lack of ulceration and secondarily through lack of terminal endbulbs.[3,4,6,7] Because of the absence of ulceration in either forms of varicella zoster ophthalmicus (VZO) epithelial keratitis, neither pseudodendrites nor their vesicular precursors stain with fluorescein, though staining with rose bengal is reported variably.[3-5,7]

Stromal/endothelial keratitis. In general, it's thought that HZO stromal keratitis represents an inflammatory manifestation of the disease rather than a true infection, though there is some controversy surrounding this. A form of deep keratitis follows the infectious episode in around 40% to 50% of cases.[3,4] The early form of this with HZO, known as nummular corneal infiltrates, occurs immediately below the previous pseudodendrite within the anterior corneal stroma and follows the infectious episode by a period of seven to 14 days.[5-7] More rarely,

About the author **Dr. Bronner** is an attending optometrist at Pacific Cataract and Laser Institute in Kennewick, WA. He has no financial interests to disclose.

an acute form of endotheliitis may also develop within this same timeframe and may cause significant corneal edema and subsequent disruption to vision. Depending on the severity of the attack, this endotheliitis could result in corneal decompensation and the need for endothelial transplantation.[3,5] Both nummular and endothelial keratitis are frequently paired with anterior uveitis.[5] While stromal disease typically follows infectious epitheliopathy, it may occur without history of a previous epithelial episode in 10% of patients.[7]

Corneal mucous plaques. A late corneal manifestation of HZO is mucous plaque keratitis (MPK). The incidence varies but is estimated at 4% to 13% and typically develops one to three months after an infectious episode, though occasionally its appearance may be delayed by years.[5,8,9] The lesions of MPK are coarse, grayish filamentous elevations weakly adherent to epithelium, and may be linear or dendriform in appearance.[8] As these are actually mucous deposits and not epithelial ulcerations, they stain negatively with fluorescein but vigorously with rose bengal.

Some sources report the lesions as having a predilection for prior foci of epithelial or stromal disease, and others report them as freely migratory.[4,5,8] Patients will be symptomatic with red, irritated eyes as a result of the mechanical shearing forces on the corneal epithelium. Culture and cytology show no viral activity.[10,11] As these are not infectious, steroids may be considered. Their efficacy, however, is variable from study to study.[4,7,9] The lesions can be manually removed, leaving behind intact epithelium, but tend to recur. The development of MPK may be linked to more serious ocular events, but their own presence is transitory, with a natural history characterized by gradual resolution leaving behind a mild underlying stromal haze.[11,12]

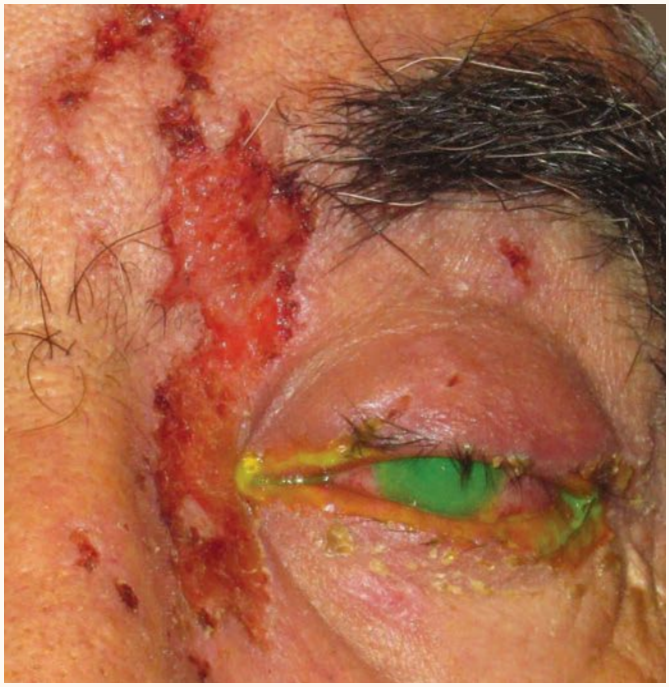

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Fig. 1. A severe episode of HZO affecting the nasociliary branch of the fifth cranial nerve. The patient has profound ocular involvement and already has a total corneal epithelial defect. The severity increases the likelihood of complex and chronic ocular involvement.

Marginal keratitis. Sclerokeratitis and serpiginous keratitis are uncommon, late manifestations of HZO, occurring one to four months after the infectious episode.[5] These are each presumed to be inflammatory responses secondary to a stromal inflammation or limbal vasculitis. Serpiginous keratitis manifests as a peripheral arcuate-shaped area of corneal ulceration and infiltration. It is often paired with localized corneal edema. As the condition progresses, thinning and vascularization take place, which may ultimately lead to perforation. The lesions have been described as similar to a Mooren's-type ulceration. Sclerokeratitis results as an inflammatory

Release Date: May 15, 2021

Expiration Date: May 15, 2024

Estimated Time to Complete Activity: 2 hours

Jointly provided by Postgraduate Institute for Medicine (PIM) and Review Education Group

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

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

- Understand the current standard of care for herpes zoster ophthalmicus.
- Understand the importance of early detection to initiate timely treatment.
- Determine when to use different treatment modalities.
- Prescribe topical steroids/antivirals appropriately.
- Recognize the role of oral antivirals in herpes zoster ophthalmicus treatment.

Target Audience: This activity is intended for optometrists engaged in routine eye care and primary care of ocular disease.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Review Education Group. Postgraduate Institute for Medicine 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 continuing education for the healthcare team. Postgraduate Institute for Medicine is accredited by COPE to provide continuing education to optometrists.

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Credit Statement: This course is COPE approved for 2 hours of CE credit. Activity #121689 and course ID 72517-SD. Check with your local state licensing board to see if this counts toward your CE requirement for relicensure.

Disclosure Statements: *Author:* Dr. Bronner has no financial interests to disclose. *Managers and Editorial Staff:* The PIM planners and managers have nothing to disclose. The Review Education Group planners, managers and editorial staff have nothing to disclose.

spillover from a preceding episode of HZO-linked scleritis. It may be seen following cases of HZO scleritis when corticosteroid therapy has been too rapidly tapered. It also may cause stromal thinning and guttering of the peripheral cornea.[4,5,7]

Disciform keratitis/corneal immune rings. These two forms of late stromal keratitis, which can occur within HZO, typically manifest months after the infectious episode. Though often discussed part and parcel with each other, they probably result from quite different immunologic scenarios.[5,10,13] The etiology of disciform keratitis is debatable and not completely defined as infectious or inflammatory, but the target is most likely the endothelium and would probably be more accurately described as disciform endotheliitis. Clinically, disciform disease is characterized by a suddenly developing circular form of corneal edema with an intact epithelium and no clearly definable infiltrate, which may have underlying keratic precipitates.[5,9,10]

Less common than disciform keratitis are corneal ring infiltrates.[5,13] Ring infiltrates are most often described in *Acanthamoeba* keratitis as one of the late stromal manifestations of that disease, but they may also be part of the clinical presentation of other sources of microbial keratitis as well as with both HSV and HZO keratitis. With viral forms, corneal rings are most typically thought to be composed of antigen-antibody complexes. When fronts of antigen migrating outward from the nidus of involvement meet a front of antibody migrating in from the limbus, the result is precipitate of an Ab-Ag complex.[11-13] Unlike microbial rings, which are generally ulcerated and apical, classic viral rings are usually not ulcerated, and their location varies.

It's important to note that the clinical appearance of many forms of HSV and HZO anterior segment disease are indistinguishable. Therefore, it is important to establish a prior history of HZO in these cases, the timing from which will aid in the diagnosis.

Natural History of HZO

Varicella-zoster virus is a member of the alpha herpesviradae family of human herpes viruses, which includes HSV 1 and 2, cytomegalovirus (CMV) and Epstein Barr virus (EBV). Like all families, the viruses that make up this group share many core similarities; in the case of alpha herpesviradae, the ability to create latency, the inability of body to fully clear the virus once initial infection has occurred and periodic reactivation are shared.

VZV causes disease during one of two states: the primary infection, known as varicella (or, more commonly, chickenpox) and secondly, an endogenous reactivation of latent VZV in the form of herpes zoster or shingles. Primary infection occurs as a result of direct contact with or via respiratory droplets from an infected individual. It manifests as chickenpox, the widely recognized itchy vesicular rash that spreads across the body.[5] Though ocular involvement here is unusual, lid and conjunctival vessels as well as dendriform corneal lesions are all occasionally encountered.[9]

Upon either vaccination or resolution of a varicella infection, the virus (the wild type or the attenuated vaccine type, depending on the source of exposure) is transported to a dorsal root ganglion of sensory nerves where, in combination with host cellular immunity, it establishes latency. About 10% to 30% of infected individuals will have latency broken and the virus will migrate from one of the ganglion reservoirs, typically resulting in the classic shingles vesicular rash respecting a dermatome.[1,5] The switch from latency to active disease seems to require some stress to host cell-mediated immunity, and the disease's increasing rate with advancing age may be tied directly to the immunosenescence, explaining the elevated risk with age.[1,2,5,43]

Interstitial keratitis. The development of significant corneal haze, vascularization and lipid deposition may follow any of the intense preceding forms for HZO keratitis. Corneal neovascularization following or as part of herpetic eye disease seems to be mediated by T-cells and, as with other forms of deep HZO keratitis, may be purely inflammatory or may be caused by a latent viral infection within the corneal stroma and may perpetuate for years.[5]

Neurotrophic disease. Neurotrophy of the cornea is a relatively common manifestation of HZO, with an estimated 20% to 45% of patients exhibiting signs of neurotrophic disease within the first year after infection, and with risk increasing following more severe episodes of HZO.[5,7,9] The clinical manifestation of corneal hypoesthesia is neurotrophic keratitis (NK), which may be mild or very severe. Classification of hypoesthesia can be performed with an esthesiometer or, as in our clinic, dental floss or cotton wisps.

The clinical picture of HZO neurotrophic disease is similar to that seen with herpes simplex, but is reported as being more severe.[5,7] Severe cases manifest as oval, "boggy" ulcerations most commonly found in the central of paracentral inferior cornea. Without successful treatment, these ulcerations may develop scarring, secondary superinfection or progressive melting, thinning and perforation.[7,9,10]

Zoster-associated uveitis. This is the second-most common manifestation of HZO, developing in up to 40% of patients.[5,9] A history of HZO increases the risk for development of uveitis by 13 times compared with the patients with shingles alone.[14] And though keratouveitis may develop twice as frequently as uveitis alone, HZO remains an important cause of isolated uveitis, particularly in an elderly population, where it may account for a high percentage of isolated uveitis cases.[14-16] When seen as an association with HZO keratitis, the uveitis follows the timeline for keratitis described above. As an isolated finding, however, it can

lag behind the acute HZO episode, in some cases by years.[16]

When seen in combination with keratitis, as a keratouveitis or endotheliitis plus uveitis, the diagnosis is generally straightforward. In the case of delayed manifestation, its clinical diagnosis is more difficult. Any unilateral uveitis in a patient over the age of 60 should prompt questioning for a recent or remote history of HZO or periocular shingles rash, among whom it accounts for a high percentage of uveitis cases. Helpful ophthalmic clues may be sectoral iris atrophy and subsequently mild corectopia, and poor direct pupillary response (with intact consensual response on fellow eye), diffusely distributed, medium-sized keratitis precipitates and ocular hypertension, though studies vary on their incidence with HZO uveitis. Ocular hypertension is also associated with a more chronic course of disease.[16,17]

Rarely, HZO can result in severe panuveitis: acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN). Each of these entities can progress to severe vision loss.[18] Among other sources of vision loss, untreated cases of ARN or PORN will go on to have profound vision loss from rhegmatogenous retinal detachment in up to 75% of cases, which highlights the importance of dilating uveitis patients to make sure there is no posterior involvement.[17,18]

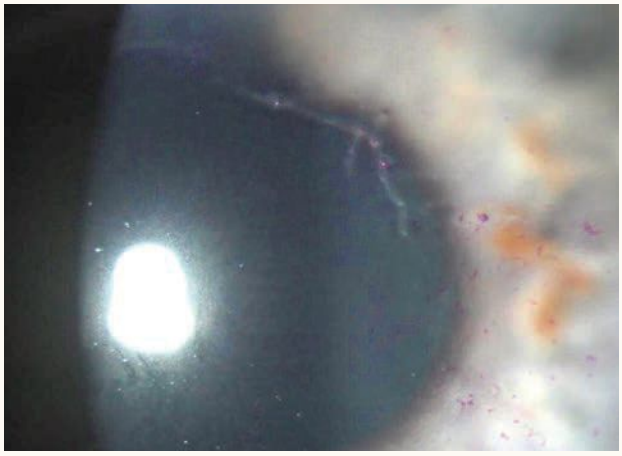

Fig. 2. Pseudodendrite seen with HZO. This occurred two weeks after the beginning of a shingles rash involving the brow of this patient. Note that the lesion is not ulcerated and only stains with rose bengal in a patchy manner.

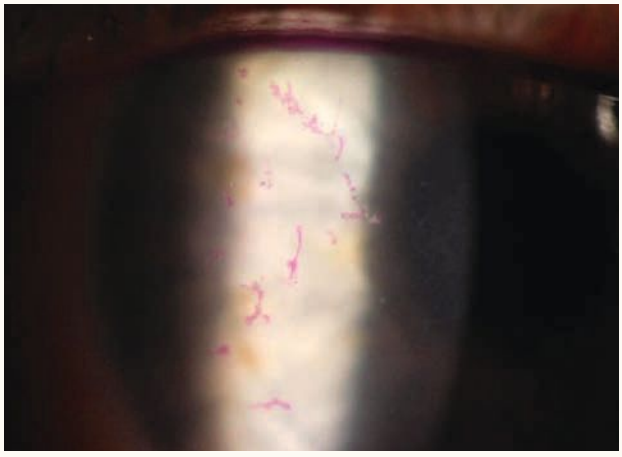

Fig. 3. Mucous plaque keratitis with HZO. This patient had a shingles episode four months prior to being referred in for eye pain. The patient did not feel the eye was involved with the initial episode. Note that these lesions, unlike the pseudodendrite in Figure 2, stain vigorously with rose bengal.

Treatment Approaches

Efforts to manage HZO can be broken down into prevention of disease, treatment of active infection, treatment of post-infectious inflammatory events and treatment of corneal neurotrophy.

Vaccination. Prevention of varicella zoster in its two forms has been accomplished with two related vaccinations. The first, Varivax (Merck), is given to infants to reduce primary infection, with good results. This vaccine has seen significant success and has reduced the incidence of varicella in at-risk populations by 70%.[5,19,20]

However, there are possible consequences of this vaccination program, primarily the unknown impact on the epidemiology of the shingles. It's speculated by some that widespread vaccination may actually increase the rate of herpes zoster at least over the short term.[19] Theoretically, people who have latent, wild-type VZV infection will see a reduction in their normal environmental exposures to VZV as a wider percentage of children are vaccinated. This then results in a reduction in immune boosting to the virus that accompanies these exposures and may manifest as increasing rates of shingles and at younger ages.[5,9,20,21]

While the jury is out on the role of Varivax in increasing the prevalence of shingles in an at-risk population, two things are not in debate: (1) the average age of patients developing shingles is decreasing and (2) the incidence of shingles is going up.[22-24] Detractors of Varivax point this out as a cause-and-effect relationship while supporters note these trends may have preceded widespread use of Varivax and can also be seen in countries without varicella vaccination programs.[22-24]

For patients at risk for shingles, Zostavax (Merck) or Shingrix (GlaxoSmithKline) should be used to reduce risk. Zostavax is a smaller dose of the same attenuated virus used in Varivax. This vaccine reduces the development of shingles by around 50%, and lowers the chances of developing severe disease and the potential for post-herpetic neuralgia as well.[25-27] Zostavax's effectiveness, however, seems to vary with patient age. Those between 60 and 69 saw a reduction in disease of 60%, but only 40% when dosed beyond the age of 70. Further, as a live virus, there is the slight risk of inducing zoster with the vaccine. Though the CDC recommended this vaccine for all people over the age of 60, its use has lagged way behind that of Varivax, with only 31% of eligible adults receiving the vaccine.[27]

The more recently developed Shingrix vaccine substitutes the live attenuated virus of Varivax and Zostavax for a viral subunit. Though efficacy of

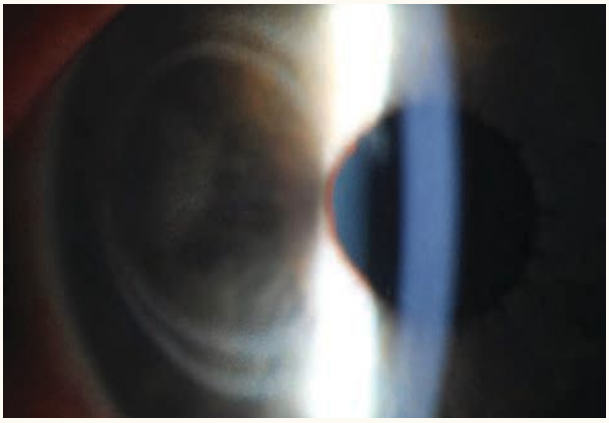

Fig. 4. A double corneal ring occurring four months following a shingles episode in a 42-year-old patient. The lesion does not stain with fluorescein or rose bengal. This issue resolved with treatment and the patient has had one further flare of HZO but has been quiet for three years.

Shringrix seems superior to Zostavax with 91% efficacy even beyond the age of 70—and, theoretically, using a viral subunit reduces potential for causing a reactivation—it is a two-dose schedule and, perhaps partially as a result of this, has failed to gain wide penetrance into the at-risk population.[26,27]

Thus far, it seems logical that shingles vaccines are perhaps best suited for patients with elevated risk of shingles but not an immediate history of it. That said, recent history of shingles does not contraindicate a booster, which may still be beneficial to the patient; in fact, the CDC recommends Zostavax in all people over the age of 60 regardless of previous episodes.[25]

Exactly how beneficial a vaccine may be after a previous episode probably relates to patient-specific factors such as immune status and the timing of vaccination relative to the episode. One author makes the case that the immune boost following an episode of shingles lasts for around three years, so recommending the vaccine three years after a flare seems reasonable.[28] Further, neither vaccine has a permanent effect and each can be repeated five years after a previous dose.

The lack of high utilization of these vaccines should be a concern within optometry and, though we generally play little role in recommending vaccinations, strongly advocating for shingles vaccination to our patients is within our purview. Keeping in mind that up to 20% of all shingles cases may involve ocular structures and each case carries the potential for debilitating, chronic or recurrent pathology to the eye, it stands to reason that as providers on the forefront of the nation's eye care, we should be actively taking a role in recommending our patients get this vaccine. Currently, the American Academy of Ophthalmology recommends that all patients 50 and older receive one or the other vaccine.[27]

Antivirals. In the late 1970s, acyclovir was developed as a highly selective, minimally toxic antiviral nucleoside analog effective in the treatment of both HSV 1 and 2 as well as VZV. The mechanism of acyclovir is to block guanosine base pairing, thereby halting DNA synthesis.[29] Acyclovir's selectivity and subsequent safety is derived from it being phosphorylated into its active form by viral thymidine kinase, and thus it only blocks DNA synthesis in virally infected cells. Acyclovir's disadvantage is its poor bioavailability; possibly only 10% is absorbed following an 800mg dose, the standard dose for VZV treatment.[30]

From acyclovir, the prodrug valacyclovir, which shows improved bioavailability compared with its parent drug, was developed.[29,30] Penciclovir, a later-developed antiviral drug, had even poorer bioavailability than acyclovir and possibly a weaker mechanism of action, but from penciclovir the prodrug famciclovir was developed, which shows a 77% bioavailability.[29,30] Ganciclovir is a related guanosine analog that has greater potential for toxicity than the other antivirals when dosed systemically and so remains a secondary option in all cases except the treatment of cytomegalovirus.[30,31]

Though these groups of medications are found to be effective in both HSV and VZV, the inhibitory concentration (IC_{50}) of acyclovir is 3µg/mL for VZV and somewhere between 0.5µl/ml and 2µl/ml for HSV 1 and 2.[30] Due to this greater concentration demand for VZV, all antivirals used in its treatment are dosed at higher levels than HSV-based disease. For example, the standard dose of acyclovir or valacyclovir for HSV is half that used for HZO (400mg five times per day for acyclovir or 500mg TID with valacyclovir for HSV keratitis) compared with that used in HZO (800mg five times per day with acyclovir/1000mg TID with valacyclovir).

The use of these medications in the treatment of HZO is established based on research with acyclovir in the 1980s, which showed benefit in reducing the duration of viral shedding and symptoms, limiting the severity of disease and reduction in late manifestations of the disease, and later studies showing a reduction in PHN.[32,33] Finally, although there is good rationale to expect guanosine analogs to be useful for VZO, the actual effectiveness of their use has been called into question. A large retrospective review found no evidence of reduction in severity of the acute episode or in the reduction of complications of the disease in patients treated with oral acyclovir (800mg five times per day) vs. those who were not treated.[34]

Theoretically, it's possible to expect that suppression dosing, found effective for HSV via the HEDS study, may also be helpful in cases of VZV, though it might be anticipated to be needed at higher dosages than those given with HSV.[35] However, no general consensus or recommendation on this matter exists and community practice is divided.[36] In the literature, I identified a couple of small reviews that support the use of low-dose chronic acyclovir. Both of these studies suggest that, in select populations the use of prophylactic therapy may result in substantial reduction of recurrence, but both studies are too limited in

design to broadly apply.[22,37] The ongoing Zoster Eye Disease Study seeks to clarify some uncertainty with the use of prophylactic antivirals but, to date, no information has been published and enrollment has been significantly below expectation.[38]

At this time, despite the lack of good data on the topic, over half of the cornea specialists polled in one review use long-term suppression therapy for chronic or recurrent HZO.[36]

Topical antivirals. Topical acyclovir may have some effect on the corneal infectious manifestations of VZV; however, the topical form of this drug is not available in the United States.[5,29] Trifluridine, an older antiviral, is effective in the treatment of infectious ocular HSV, but is not effective against HZO and so should not be used.[5] Therefore, until recently there were no available products to be used topically against HZO. This may have changed with the release of Zirgan (ganciclovir 0.15% gel, Bausch + Lomb). A small case series suggests that the use of topical ganciclovir may have shortened the duration of the disease.[39] While this study does not provide extremely strong evidence of effect, we know that ganciclovir does have efficacy against VZV, which makes its topical use a reasonable adjunct in some cases of HZO, particularly during the actively infectious stage manifesting with pseudodendrites.[30]

Corticosteroids. The use of corticosteroids in cases of corneal HZO is an area of debate and is even more controversial than in HSV, where at least in stromal and endothelial disease it is felt to be a required component of treatment as determined by the HEDS study.[40] In McGill's article from 1987 on the uncertain mechanisms of both simplex and varicella zoster etiologies of stromal keratitis, the suggestion is made that injudicious treatment with corticosteroids may prolong episodes and promote recurrence.[6] This advice is echoed in Holland's *Cornea*; Dr. Lee acknowledges the effectiveness of corticosteroids to treat these manifestations on one hand, but on the other recommends they should be avoided, when possible, given the potential for extending the duration of disease beyond its normal course.[5]

Despite the mini controversy surrounding their use, these recommendations against their use do not appear to be explicitly followed in clinical practice. The most widely used treatment modality for HZO is a combination of topical corticosteroids and oral antivirals, according to one review on practice patterns among cornea specialists.[36] At our clinic, we treat cases of HZO with steroids when reduction in vision is likely to occur in their absence, which would be cases of significant stromal/interstitial disease, corneal endothelial disease and uveitis but generally not epithelial disease. The dosage of steroid varies on a case-by-case basis, but generally we will seek to use the lowest dose of steroid that allows total elimination of clinical inflammation.

Treatment of neurotrophic disease. NK may be one of the most troublesome and recalcitrant forms of zoster-related keratitis to manage. While ulcers and epithelial disturbances associated with neurotrophy can wax and wane over the disease course, unless the underlying level of corneal hypoesthesia remits, the problems will recur. Treatment varies and can include lubrication, punctal occlusion with either plugs or cauterization, bandage contact lenses—often used chronically—amniotic membrane, autologous serum eye drops, scleral contact lenses, Oxervate (cenegermin, Dompé), tarsorrhaphy and conjunctival/Gunderson flaps.[41,42]

While conservative therapy is helpful in mild and acute manifestations, long-term management of NK in unremitting recurrent cases should use long-term solutions, either a scleral contact lens, a conjunctival flap (where the visual potential is limited), a partial or full tarsorrhaphy or perhaps Oxervate. When considering Oxervate for long-term management of NK, it's important to recognize that it has not been shown to increase corneal sensitivity, the underlying mechanism of NK, but only to speed the healing of the ulcer itself.[42] Our clinic has used the medication in recalcitrant cases of NK to good effect with positive responses in both the acute phase (healing the ulcer) and the chronic phase (preventing re-ulceration).

Conclusion

Herpes zoster is a systemic infectious disease with a moderately high predilection for the ocular and periocular tissue. When the trigeminal nerve is affected, ophthalmic findings frequently manifest. These manifestations are extremely variable, though they seem to follow a predictable timeline. Early-stage findings such as epitheliopathy may resolve and give way to mid-stage findings such as nummular keratitis. These in turn may become disciform keratitis, or in more serious cases serpiginous disease. Within the eye, iritis and panuveitis may develop. Essentially, any unusual unilateral red eye in a patient with a history of ipsilateral

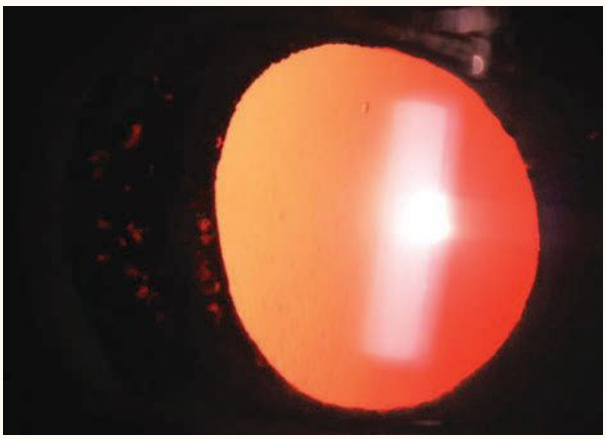

Fig. 5. Iritis in HZO. The iritis in this eye developed about two months after the episode of MPK seen in Figure 3. The patient had modest AC reaction, sectoral iris atrophy and a distorted, poorly reactive pupil (this photo is in a non-dilated eye). Two years later, the patient is still unable to come off of steroids without a flare-up of their disease.

Photo used with permission of Brian Johnson, OD

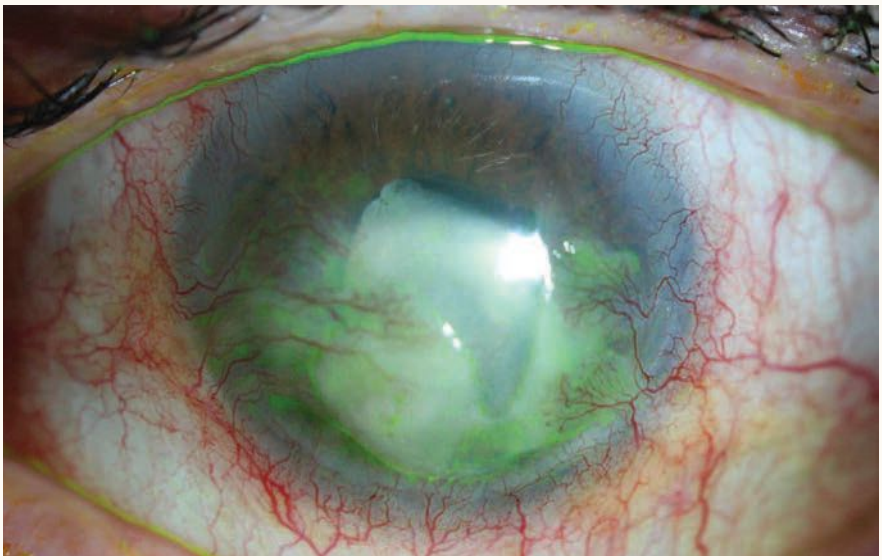

Fig. 6. This is the patient from Figure 1. After years of dealing with unremitting zoster-related inflammation, iritis and neurotrophy, the patient's cornea opacified and vascularized, and the pupil became irregular and non-responsive. His case illustrates the potentially catastrophic impact of HZO on the visual system.

shingles in the preceding six months should have HZO on the differential.

Though use of antivirals in the acute, infectious stage is widespread, treatment approaches in the later, post-infectious stages are more varied. The potential for chronic and recurrent disease are particularly troublesome and can leave the clinician stumbling along a poorly defined treatment algorithm. Further, for one reason or another, shingles is becoming more common and occurring at a younger age.

This highlights perhaps the most important thing optometrists can be doing in the management of HZO—start helping to prevent the disease. As a profession, we need to be vocal with our patients in promoting the use of one of the two available shingles vaccines. An ounce of prevention is worth a pound of cure after all, particularly when the "pound of cure" is not well defined or even particularly effective, as is the case with much of our management options with HZO once the disease has taken hold. ■

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OPTOMETRIC STUDY CENTER QUIZ

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1. Which is NOT true of alpha herpes viruses?
a. They target humans.
b. The body is able to effectively clear the virus.
c. Initial infection is followed by a period of latency.
d. Broken latency results in recurrent disease.

2. By what percent has Varivax reduced chickenpox in the US among the at-risk population?
a. 30%.
b. 60%.
c. 70%.
d. 100%.

3. In the US over the last 25 years, what trends have been seen with shingles epidemiology?
a. Less frequent and occurring later in life than in previous generations.
b. Less frequent but occurring earlier in life than in previous generations.
c. More frequent and occurring earlier in life than in previous generations.
d. More frequent but occurring later in life than in previous generations.

4. Which is NOT true regarding shingles?
a. The most frequently involved area is along the trunk.
b. The most frequently involved cranial nerve is the facial nerve.
c. Involvement of the nasociliary nerve increases the likelihood of ocular involvement.
d. The incidence of shingles increases with increasing age.

5. Which statement most accurately conveys chronology-based differences between HSV and VZV ocular disease?
a. The varied ophthalmic manifestations of VZV follow a specific chronology relative to the time from the original flare-up, while HSV does not.
b. Neither VZV nor HSV follows a specific chronology with their ophthalmic effects.
c. The varied ophthalmic manifestations of both VZV and HSV follow a specific chronology relative to the time from the original flare-up.
d. The varied ophthalmic manifestations of HSV follow a specific chronology relative to time from the original flare-up, while those of VZV does not.

6. Which of the following is FALSE in describing the timing of the various manifestations of HZO?
a. Epithelial disease is an early finding of the disease.
b. Mucous plaque keratitis follows the initial infection days later.
c. Stromal disease may immediately follow epithelial disease.
d. Interstitial keratitis may simmer for years following the initial episode.

7. Which is TRUE of pseudodendrites with HZO?
a. They are a late manifestation of the disease.
b. They will not clear without antiviral therapy.
c. They lead to geographic ulceration if untreated.
d. Unlike HSV dendrites, pseudodendrites are not true ulcerations.

8. Which is TRUE of stromal keratitis with HZO?
a. It is universally accepted to be an inflammatory manifestation.
b. It is universally accepted to be an infectious manifestation.
c. It is frequently paired with anterior uveitis.
d. It occurs in only 10% of patients with preceding epithelial disease.

9. Mucous plaque keratitis in HZO _____.
a. Often follows the original episode by months.
b. Can be permanently removed at the slit lamp.
c. Is a reactivated viral process.
d. Generally causes no symptoms.

10. Which is FALSE regarding HZO-associated marginal keratitis?
a. It is a late manifestation of HZO and typically follows the initial episode by months.
b. It is due to an incompletely treated infection and represents reactivation of a perpetuating infection.
c. It may lead to perforation.
d. It is a severe manifestation and can behave somewhat like a Mooren's ulcer.

11. HZO disciform keratitis _____.
a. Clinically looks like HSV-linked disciform disease.
b. Generally, immediately follows epithelial keratitis.
c. Will be paired with significant stromal infiltration.
d. Is caused by reduction in corneal sensitivity.

12. Corneal rings from HZO _____.
a. Are generally ulcerated and apical.
b. Are typically composed of infiltrating T-cells and virally infected cells.
c. Usually occur within a few days of the initial episode of HZO.
d. Are a precipitate of antigen-antibody complex.

13. Which is TRUE regarding corneal neurotrophy following HZO?
a. 90% of patients will develop clinical signs of neurotrophy.
b. Is a mild form of the disease to treat.
c. Seems related to the initial episode's intensity.
d. Is less severe than HSV-induced neurotrophy.

14. Which is FALSE about HZO-linked uveitis?
a. May lead to a retinal detachment.
b. May account for a significant percentage of all uveitis cases among the elderly.
c. Corectopia may be a clue that an iritis is viral in origin.
d. Typically is both bilateral and granulomatous.

15. Which best describes the available shingles vaccination options?
a. Both effectively reduce the incidence of shingles.
b. Shingrix has a higher rate of inducing an episode of shingles than does Zostavax.
c. Zostavax is a two-step vaccine.
d. Shingrix does not perform as well as Zostavax in patients over age 70.

16. Which is FALSE regarding the shingles vaccines?
a. The CDC recommends for all patients over age 60.
b. The American Academy of Ophthalmology recommends for all patients over age 50.
c. The vaccines have been widely used by the susceptible population.
d. The vaccines may reduce incidence of shingles by up to 90%.

17. Which is true regarding antivirals for HZO?
a. Topical trifluridine is a front-line treatment.
b. There is at least some evidence that oral acyclovir is NOT effective in reducing severity and complication rates.
c. There is no clinical or even theoretic support for the use of topical ganciclovir.
d. Acyclovir is a pro-drug of valacyclovir and improves its bioavailability.

18. Which statement is FALSE regarding the role of acyclovir in prophylaxis of HZO?
a. Acyclovir may have a role in the management, but strong prospective evidence does not exist.
b. The HEDS study showed that low-dose oral acyclovir reduced the risk of recurrence of HZO.
c. Small retrospective reviews have shown some benefit of prophylactic acyclovir.
d. The ZEDS study is seeking to answer questions surrounding the role of oral acyclovir in the prophylaxis of HZO but is ongoing.

19. Which best describes the role of steroids in management of HZO?
a. Always recommended for HZO corneal disease.
b. Sometimes used in treatment of HZO corneal disease.
c. Never recommended in treatment of HZO corneal disease.
d. There is a consensus of expert opinion on the role of steroids in HZO.

20. Which statement regarding the treatment options for neurotrophic keratitis following HZO is TRUE?
a. Amniotic membrane may be useful in healing resultant corneal ulcers.
b. The nerve growth factor Oxervate has been proven to re-establish normal corneal sensitivity.
c. A conjunctival flap is considered front-line therapy.
d. Priming the ocular surface with preservative-free tears, punctal occlusion and ointment is outdated and no longer has a role in neurotrophic keratitis.

Examination Answer Sheet

Get to Know HZO

Valid for credit through May 15, 2024

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Answers to CE exam:

1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
3. Ⓐ Ⓑ Ⓒ Ⓓ
4. Ⓐ Ⓑ Ⓒ Ⓓ
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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. Understand the current standard of care for herpes zoster ophthalmicus. ① ② ③ ④ ⑤
22. Understand the importance of early detection to initiate timely treatment. ① ② ③ ④ ⑤
23. Determine when to use different treatment modalities. ① ② ③ ④ ⑤
24. Prescribe topical steroids/antivirals appropriately. ① ② ③ ④ ⑤
25. Recognize the role of oral antivirals in herpes zoster ophthalmicus treatment. ① ② ③ ④ ⑤

26. 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.

27. 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): ☐

28. 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: _____

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

Ⓐ Very confident Ⓑ Somewhat confident Ⓒ Unsure Ⓓ Not confident

30. 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: _____

31. Additional comments on this course: _____

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Rate the quality of the material provided:

1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

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.

Signature _____ Date _____ Lesson 121183 RO-OSC-0521

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Sidestep Side Effects

Here's how to minimize the potential complications of a KPro.

Q I have a few patients with a keratoprosthesis (KPro). What does this procedure involve? What form of prophylaxis is recommended to reduce risk of complications?

A "The most common artificial cornea used today is the Boston KPro," says Larae Zimprich, OD, of Vance Thompson Vision. A KPro is indicated in poor candidates for PKP due to reasons such as repeated graft failure, aniridia, Stevens-Johnson syndrome, chemical burn and autoimmune disease, in which there is often complete or nearly complete stem cell deficiency.

Since FDA approval in 1992, more than 12,000 patients have been implanted with a KPro.[1] The most widely used (Type I) is for patients with adequate or normal tear function.[2] Type II is reserved for end-stage corneal disease and requires a permanent tarsorrhaphy.[2]

The KPro Type I consists of a clear PMMA front plate, a back plate of titanium or PMMA that contains 16 fenestrations to allow passage of nutrients, and a locking ring behind the plates to secure the system.[2] The corneal graft is situated between the two plates.[2]

The Procedure

KPro insertion typically takes 1.5 hours. Patients are monitored under general anesthesia or a retrobulbar block.[3] First, a surgeon marks the center of the host cornea by using a Sinskey hook and measures the cornea to determine the appropriate transplant size. Then, the KPro is assembled. A donor cornea with a 3mm central hole is sandwiched between the front and back plates. The locking ring binds the system together.

Next, the surgeon trephines the recipient's cornea. A paracentesis is created for injection of viscoelastic into the anterior chamber to maintain structure and stability. The KPro is then sutured into place with at least 12 uninterrupted or running 9-0 nylon sutures. Once the sutures are buried and Seidel-negative, a bandage contact lens is placed on the eye. Following surgery, an antibiotic and a steroid are injected into the conjunctiva.[2]

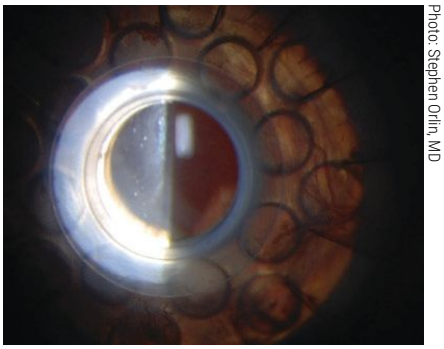

Photo: Stephen Orfin, MD

Retroillumination view of the fenestrated back plate on the Boston KPro.

Post-surgical complications such as retroprosthetic membranes, glaucoma, cataracts, infection, retinal detachment, device extrusion and stromal necrosis can occur. For this reason, other procedures can be combined with the KPro, such as cataract removal or IOP-lowering device implantation. Educate patients on the risk of adverse effects and the associated prognosis.

Follow-up

Long-term care by different specialists, including cornea, glaucoma and retina, is required for patients with a KPro, according to Dr. Zimprich. One of the most common complications is endophthalmitis. To date, the overall incidence of endophthalmitis is 2.7%, which is 67.5 times greater than the rate associated with cataract surgery.[2] To decrease endophthalmitis risk, a cocktail of medications is typically administered during surgery and continued prophylactically over a patient's lifetime.

While there's controversy over which antibiotic should be taken long-term, a broad-spectrum, fourth-gen fluoroquinolone (moxifloxacin or gatifloxacin) is most commonly used, says Dr. Zimprich. In autoimmune or monocular patients, fortified vancomycin is prescribed. These should be taken QD.[4]

Following surgery, patients require long-term bandage contact lens wear to prevent surface dehydration and enhance graft retention, notes Dr. Zimprich. Consequently, fungal keratitis is more likely to occur. Prescribe patients amphotericin B (0.15%) or natamycin (5%) to use as needed.[4] Lens removal and replacement every three months or so is crucial.[4] Betadine is recommended before lens reinsertion.

Lifelong topical steroids (*e.g.*, prednisolone acetate) are required in all KPro eyes, says Dr. Zimprich. After the initial post-op period, taper down to once daily.[4] Close monitoring is necessary, as steroids can exacerbate infection. If irritation occurs, patients should stop steroid use and see an eye specialist immediately.

Repeat all glaucoma tests every six months, suggests Dr. Zimprich. The central cornea is no longer intact; therefore, measure IOP every three months using a tactile approach. This is why many surgeons implant an IOP-lowering device in glaucoma suspects.[4] ■

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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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SCAN ME

From Dislocation to Restoration

This patient had to undergo IOL replacement surgery to finally achieve satisfactory vision.

BY LEONID SKORIN, JR., DO, OD, MS
MINNEAPOLIS

A 75-year-old male presented with sudden vision loss in his left eye that had occurred earlier that same day. He reported that his vision was somewhat clearer in the periphery than centrally. There were no accompanying flashes and, although he had a history of floaters, they did not increase in incidence with the loss of vision. He denied eye pain, new-onset headache and jaw claudication. He had not experienced any trauma.

Case

The patient's ocular history included open-angle glaucoma, for which he was using latanoprost 0.005% in each eye at bedtime. He was also pseudophakic in both eyes. He had phacoemulsification cataract surgery with posterior chamber (PC) intraocular lens (IOL) implantation 27 years earlier. At that time, he was corrected for monovision, with his right eye set for distance and his left eye set for near. He noted that he had never been satisfied with his monovision prescription. He also had YAG laser capsulotomies in both eyes 16 years ago. His medical history was positive for benign prostatic hypertrophy, for which he was taking tamsulosin.

The patient's entrance acuities with his current glasses were 20/20-1 OD and count-fingers at six feet OS. His vision improved to 20/175 OS with pinhole, but he was still unable to see the near-point chart with his near-corrected left eye. Manifest refraction of the left eye yielded 20/20-2 with a +6.00D sphere lens. Pupils, extraocular motility and confrontation visual fields were normal. Intraocular pressures were 13mm Hg OD and 14mm Hg OS.

The slit lamp exam showed a stable posterior chamber IOL in the right eye. There was an apparent void with no PC-IOL seen behind the pupil of the left eye. Otherwise, the anterior segments of both eyes were unremarkable. The fundus exam found an optic nerve cup-to-disc ratio of 0.75 but was otherwise unremarkable. The posterior chamber IOL was not visible in the vitreal cavity of the left eye; only when the patient was placed in Trendelenburg's position did it finally emerge. The PC-IOL was still within the capsular bag and attached by zonules at the six o'clock position, causing a hinge-like phenomenon. It positioned itself inferiorly when the patient sat up. This was confirmed with anterior segment B-scan ultrasonography (*Figure 1*).

We were able to review the patient's eye records from 32 years prior. He was a moderate myope in both eyes. His pre-cataract surgery glasses correction was -5.00+1.25x082 OS, and his keratometry measurement was 40.25x41.12 OS. We found that he had significant axial myopia OS, with an A-scan measurement of 28.48mm (axial myopia defined as axial length >26.00mm). Nowhere was there any indication of pseudoexfoliation (PEX) or uveitis history. The patient did not have any connective tissue disorders.

Discussion

IOL dislocation is an uncommon complication following cataract surgery. With respect to time, posterior chamber IOL dislocation is divided into early and late cases. Early cases occur within the first three months of cataract surgery, while late cases happen after.[1,2] In general, early cases of PC-IOL dislocation are the result of inadequate posterior chamber IOL fixation within the capsular bag but can also result from a zonular rupture during a traumatic cataract surgery.[3,4] Late cases result from progressive zonular weakness and capsular bag contraction years after even uncomplicated cataract surgery.[5]

More specifically, posterior chamber IOL dislocation can be divided into five catagories:[6]

- A lens that is decentered within an intact capsular bag. This is most often seen in patients with PEX.
- A lens that is partially subluxed out of the capsular bag, with one haptic in the bag and one haptic out or one haptic in and the optic and other haptic out. This can also result in uveitis-glaucoma-hyphema (UGH) syndrome.
- A lens that is in the ciliary sulcus. An IOL is surgically positioned in the sulcus if there is a compromised capsular bag, meaning there is a tear in the posterior capsule or rupture of the equatorial capsule. Posterior chamber IOL dislocation in this case is referred to as sunset (inferior displacement) or sunrise (superior displacement) syndrome.[2]

About Dr. Mangan **Dr. Mangan** is a board-certified consultative optometrist from Boulder, CO, and a fellow of the American Academy of Optometry. He is an assistant professor in the department of ophthalmology at the University of Colorado School of Medicine. His focus is on ocular disease and surgical comanagement. He has no financial interests to disclose.

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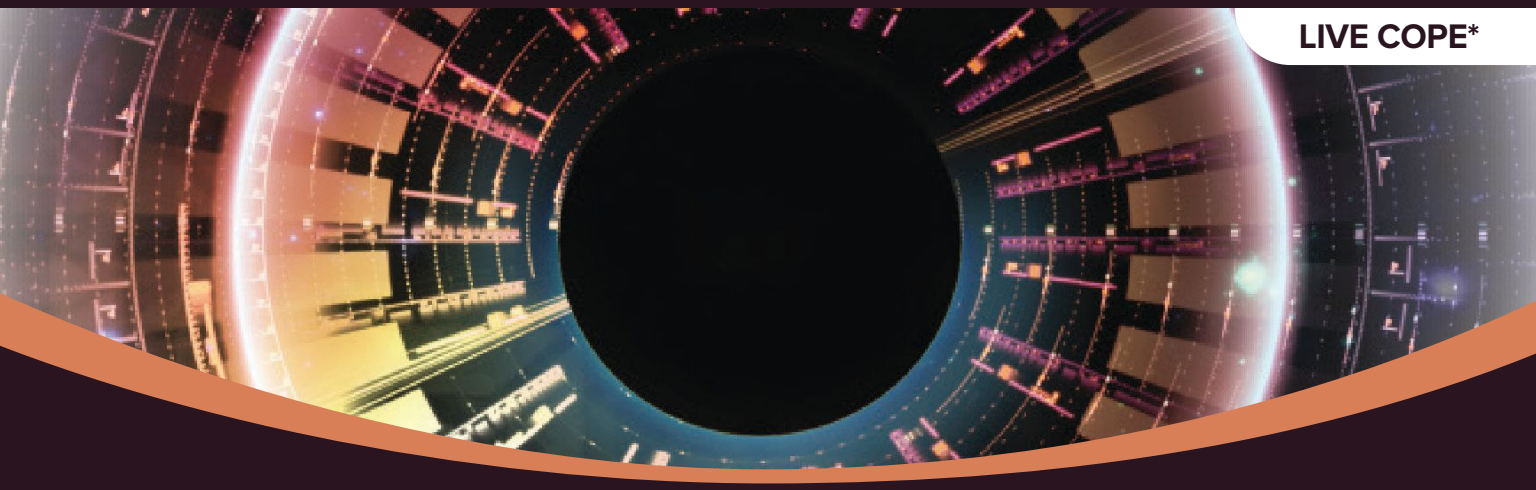

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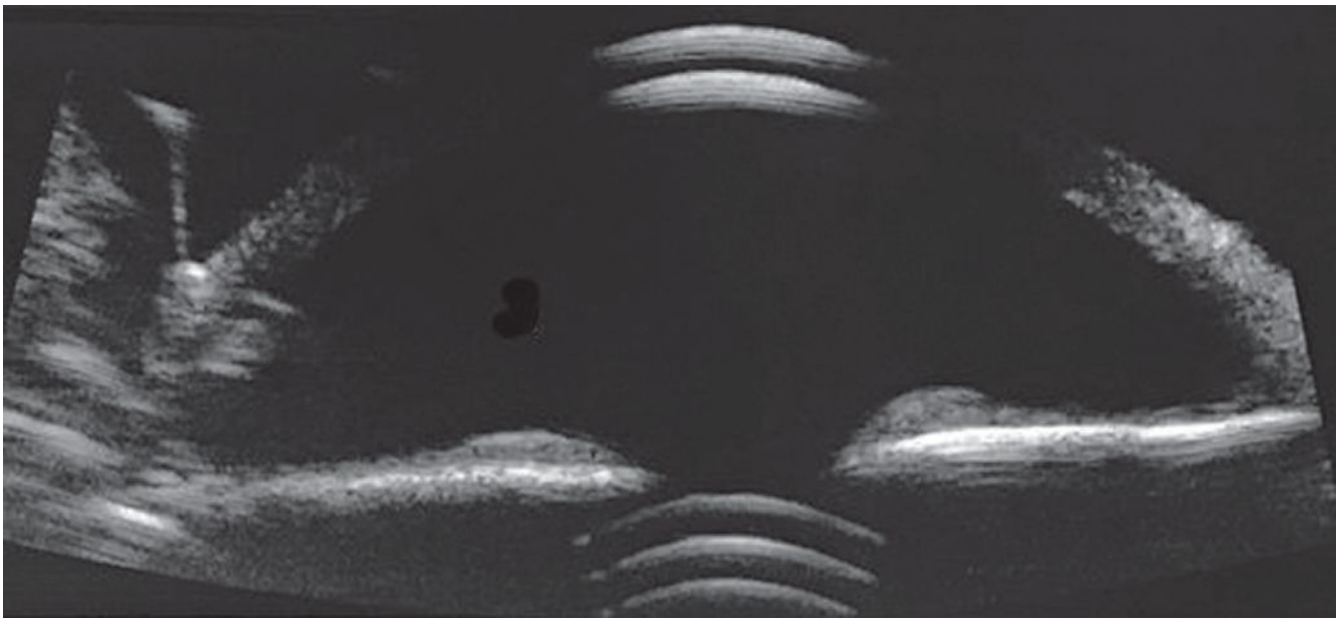

Fig. 1. Reverberations of sound waves can be seen from the dislocated posterior chamber IOL/capsular bag complex behind the iris.

• A PC-IOL that's in the capsular bag, both of which are dislocated. This is what our patient presented with.

• A PC-IOL dislocated into the vitreal cavity or sitting on the retina.

The first three categories are usually seen within the first three months after cataract surgery (early cases), while the last two usually occur in late cases.

Late, spontaneous PC-IOL dislocation occurs with a cumulative rate of 0.1% after 10 years and 1.7% after 25 years.[2] One study found late-case PC-IOL dislocation occurred with virtually all posterior chamber IOL materials and lens designs.[7] The same series found that PEX accounted for 50% of all PC-IOL dislocations.[7]

Other causes included high myopia, trauma, vitreoretinal surgery, retinitis pigmentosa, connective tissue disorders, diabetes, atopic dermatitis, previous angle-closure attacks and even older age, as zonules become more friable with age.[2,7] Any condition, including uveitis, that results in the breakdown of the blood-aqueous barrier is also likely to be associated with progressive zonulysis and potentially late-case PC-IOL dislocation.[8]

Management

Surgery for secondary IOL implantation in the absence of capsular support may include an anterior chamber IOL, an iris-fixed IOL, a transscleral, sutured PC-IOL or a flanged, intrascleral PC-IOL fixation technique.[9] In one study, dislocated, in-the-bag PC-IOLs were replaced with anterior chamber IOLs in 60% of patients or repositioned or exchanged and then fixed to the sclera in 40% of patients.[1] Surgeons usually try to reuse the current PC-IOL if it is not damaged and if the patient reacted well up until the dislocation.[8]

Our patient was never satisfied with his monovision correction, so he chose a lens exchange with the new posterior chamber IOL to be set for optimal distance correction.

The corrective surgery was performed with the assistance of a retina surgeon. The surgeon performed a vitrectomy and prolapsed the dislocated posterior chamber IOL/capsular bag complex into the anterior chamber. This lens/bag complex was then removed through a temporally placed scleral tunnel incision. A three-piece acrylic monofocal posterior chamber IOL was passed through this same surgical incision and into the anterior chamber. It was then maneuvered into the posterior chamber with its two haptics externalized through the sclera and secured using the flanged, intrascleral fixation technique.[9]

At the three-month post-op visit, the patient was no longer on any post-op medications. His uncorrected distance vision was 20/30+2 OS. With a refraction of -0.50 +0.50x174 OS, he was able to see 20/20-1 OS. A +2.50 add yielded 20/20 OS at near. He was happy he did not need distance glasses and satisfied that he only had to use simple reading glasses for near work. ■

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ABOUT THE AUTHOR

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Persistent Proliferation

Solve this patient's cloudy vision with fundus photography.

BY RAMI ABOUMOURAD, OD
HOUSTON

A 56-year-old Hispanic male presented with a two-week history of "blurry vision" in his left eye. He described a cloudiness and fogginess to his vision and a left-sided dull, achy eye pain. Upon further questioning, he endorsed a three-week history of flashes and floaters in the left eye. The right eye was asymptomatic and he denied any similar previous episodes in either eye. His past ocular, medical and social histories were unremarkable. He had no known drug allergies and did not remember his last eye exam.

On examination, his best-corrected visual acuity (BCVA) was 20/25-1 OD and hand motions OS. There was a relative afferent pupillary defect in the left eye. His extraocular motilities were full OU, and there was a significant constriction to his confrontation visual fields OS. His intraocular pressure (IOP) measured 18mm Hg OD and 4mm Hg OS. Anterior segment examination revealed a deep anterior chamber (AC) OU with rare cells and 1+ flare OS. Imaging of the posterior segment is shown below (*Figure 1*).

Take the Retina Quiz

1. Which is seen in the fundus photo?
a. A retinal tear or retinal detachment (RD).
b. A choroidal detachment.
c. Pre-retinal membranes.
d. All of the above.

2. Which of the following is true of the membranes in the fundus photos?
a. They are secondary to retinal pigment epithelial cell proliferation.
b. They are secondary to chronic retinal ischemia.
c. They are fibrovascular in origin.
d. They can be treated with intravitreal anti-VEGF therapy.

3. What is the strongest preoperative risk factor for surgical failure of RD repair?
a. Acute macular involvement.
b. Proliferative vitreoretinopathy (PVR).
c. Vitreous hemorrhage.
d. None of the above; there is a 100% success rate of RD repair.

4. Which of the following is true of rhegmatogenous retinal detachment (RRD) repair?
a. Smaller-gauge surgical instrumentation yields a better prognosis.
b. Intravitreal steroid use yields a better prognosis.
c. Cigarette smoking yields a poorer prognosis.
d. Perfluoropropane (C_3F_8) gas always yields a poorer prognosis than silicone oil.

5. What level of VA will most patients achieve in the setting of postperative anatomic success?
a. Approximately 20/50 BCVA.
b. Ambulatory vision (approximately 20/800).
c. Light perception.
d. No light perception.

For answers, see page 106.

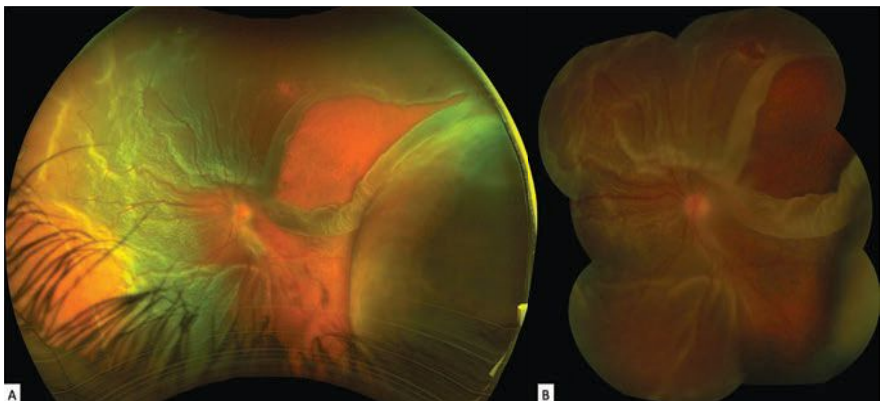

Fig. 1.Optos ultra-widefield (A) and Topcon (B) montage fundus images of the left eye.

Diagnosis

Slit lamp examination of the patient revealed positive Shafer sign in the left eye with pigment clumping in the inferior vitreous and moderate vitreous haze. Fundus exam revealed a large radial superotemporal retinal tear with an adjacent smaller break at 12:30 in the left eye, with bullous surrounding subretinal fluid (*Figure 1*). The macula was detached, and there were diffuse preretinal tractional membranes anterior and posterior to the equator. There remained only a small sector of attached retina inferotemporally (*Figures 1B and 2*). Additionally, there were serous choroidal effusions nasally and temporally (*Figure 1*).

We diagnosed an RRD with PVR OS. The size and chronicity of the large retinal tear led to secondary hypotony

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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with choroidal effusions, AC inflammation and ciliary body shutdown—resulting in the patient's eye pain.

Discussion

PVR is defined as the avascular proliferation and contraction of fibrocellular retinal membranes associated with a rhegmatogenous retinal detachment.[1,2] Despite surgical advances, PVR remains the leading cause of rhegmatogenous retinal detachment (RRD) surgical failure at a rate of 5% to 10% (mean of 7%).[1-4] Risk factors for PVR development include retinal tear size, presence of vitreous hemorrhage, chronic intraocular inflammation, longstanding untreated RRD, unsuccessful RRD repair and penetrating ocular trauma.[1,3-6] While its role is not completely understood, smoking is the only identified modifiable risk factor for PVR development.[7]

Disruption of the blood-retinal barrier—as in the case of a retinal break or detachment, uveitis, cryotherapy and trauma—allows for the influx of inflammatory and retinal pigment epithelial (RPE) cells into the vitreous cavity.[5,6] Once liberated, the proliferation of these cells leads to formation of preretinal and subretinal membranes.[2] Proliferative membranes, once formed, contract and induce retinal traction.[2] The tractional forces exerted from these membranes can create secondary retinal breaks as well as reopen breaks that have already been treated.[2] These secondary breaks in the retina serve as a conduit for further influx of catalytic RPE and inflammatory cells.[2] As demonstrated, the pathogenesis of PVR is cyclic and self-propagating.

Clinically, the retina takes on an opaque appearance with wrinkles and fixed folds.[2] Due to gravity, PVR tends to begin inferiorly with fine membranes bridging the retinal folds as they contract. Often, one can appreciate proliferative membranes at the leading edge of a retinal break, which causes stiffening of the torn retina and a rolled posterior edge. Dynamic ultrasonography remains a powerful tool for identifying advanced PVR by evaluating the mobility and rigidity of the retina, which can aid prognostication and surgical planning.[5] Retinal rigidity can also be assessed during scleral depression, and by evaluating retinal mobility during saccades on indirect ophthalmoscopy.[1,5]

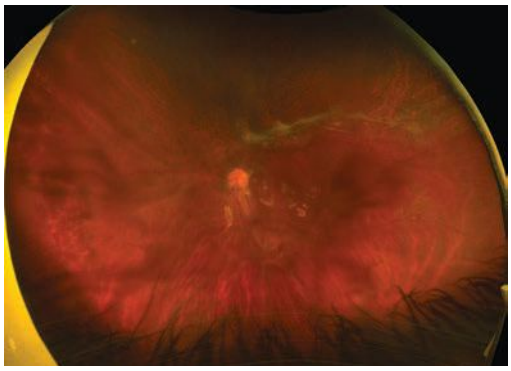

Fig. 2. Ultra-widefield fundus image of the left eye at post-op month two.

Early PVR is characterized by vitreous haze, pigment clumping and retinal folds, and advanced PVR became further subdivided in a more recent classification after surgical success rates were better for posterior than anterior PVR.[3,4] Many clinicians still simply grade PVR as mild, moderate or severe and acknowledge anterior/posterior extent of starfolds and traction.

Treatment Options

Surgical intervention remains the primary treatment modalities for these complex eyes.[8] Pars plana vitrectomy (PPV) has been performed using 20-, 23-, 25- and 27-gauge instrumentation with equivalent outcomes.[3] A thorough vitrectomy with complete removal of the vitreous and any preretinal membranes is necessary to achieve optimal outcomes.[3] Comparison of intraocular tamponades revealed that silicone oil and perfluoropropane (C_3F_8) gas are both equivalent to each other but superior to sulfur hexafluoride (SF_6) gas.[9,10] Subgroup analysis, however, suggested better visual prognosis with silicone oil for eyes with anterior PVR.[10]

Unfortunately, the prognosis for these complex RRDs remains poor despite best surgical efforts. The retinal redetachment rate can be as high as 75% depending on preoperative severity.[8] Reported anatomic success rate in these cases is 60% to 80%.[8] Of those that are anatomically successful, only 40% to 80% will recover ambulatory vision (5/200) or better.[6,8]

The patient in question was referred to our retina service. Understanding the risks, benefits and alternatives to treatment, the patient underwent 25-gauge PPV, endoscopic laser photocoagulation, membrane peel, fluid-air exchange, cryotherapy and insertion of 5000-centistoke silicone oil.

On the first day of post-op, the patient's vision was counting fingers at three feet and IOP was 4mm Hg. There was good silicone oil fill, and the retina was grossly flat under the oil with fresh laser surrounding the superotemporal retinal breaks. The patient was then lost to follow-up until month two of post-op, at which his vision remained at counting fingers and IOP was 17mm Hg. The retina remained attached under oil with an epiretinal membrane along the inferior arcade inducing traction (*Figure 2*). ■

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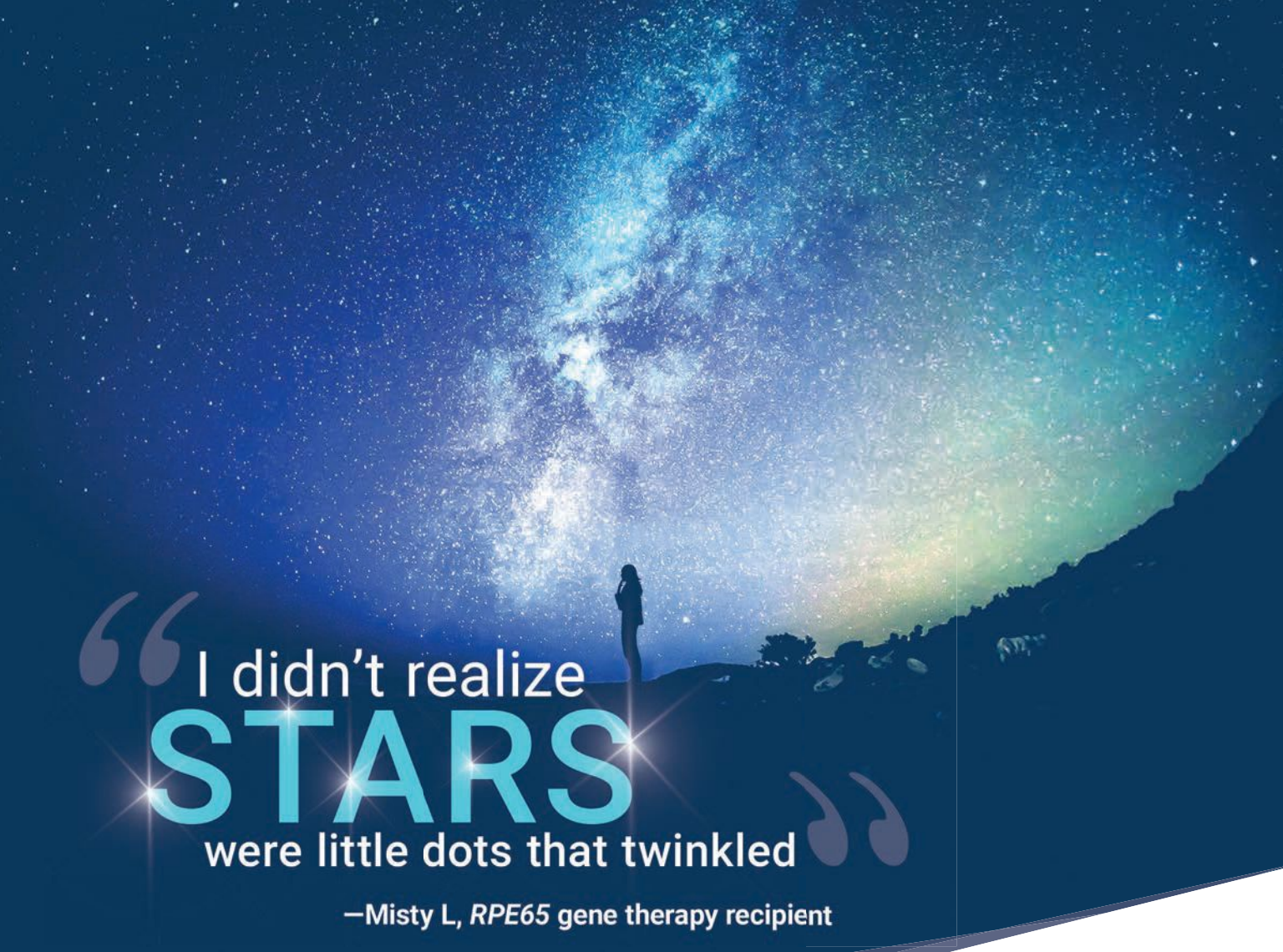

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▶ DRY EYE TREATMENTS

Preservative-free Artificial Tear Now Multidose

Dry eye patients generally prefer preservative-free topical products, as agents like benzalkonium chloride can exacerbate ocular surface compromise, but they also enjoy the convenience of reusable bottles. Alcon seeks to serve both goals with its recent introduction of Systane Hydration Multi-Dose Preservative-Free (MDPF), which puts its popular ocular lubricant in a specially designed bottle. The tip of the device is equipped with a one-way valve that blocks uptake of fluid back into the bottle to help prevent contamination, allowing the product to remain preservative-free. Alcon calls this bottle design "PureFlow."

Dry eye patients and those who've recently undergone surgery often use ocular lubricants multiple times per day, and this new packaging aims to ease their experience of it, Alcon said in a press release. The product itself, intended for aqueous-deficient dry eye patients, contains both sodium hyaluronate and HP-Guar polymers (a pairing Alcon calls "HydroBoost") to help achieve long-lasting relief, the company explains.

Systane Hydration MDPF will soon be available through retail outlets, the company says. The product is also available in single-use vials, introduced last year.

New IPL Device Offers Greater Control

Patients with meibomian gland dysfunction who are looking for a more long-lasting treatment than that of topical products are amenable to various in-office procedures, including the application of intense pulsed light (IPL) to reduce inflammation and aid expression of clogged glands. A new IPL device from Lumenis, called OptiLight, was recently cleared by the FDA and will be launched this month.

A press release says the device significantly improved tear breakup time, meibum quality and gland expressibility in a randomized controlled trial. OptiLight includes what Lumenis calls optimal pulse technology, which it says gives users the ability to control the pulse shape, provides reproducible results and creates more comfortable treatments.

▶ PRODUCT PREVIEWS

J&J Preps Entry into Myopia Control Market

Increased attention to the global prevalence of myopia is motivating doctors, parents and manufacturers to respond. The latest entrant is Johnson & Johnson Vision, which recently announced plans to offer resources, products and services under the name Acuvue Abiliti by the end of this year. No specific items have been announced yet, but a company press release alludes to annual purchases of Abiliti products. The company says these transactions will help provide a free comprehensive eye exam for needy children through Sight for Kids, a joint program from the company and the Lions Club.

The move follows the recent announcement of a partnership between J&J and Menicon to address myopia wherein Menicon will develop products and J&J will assist in distribution to broaden their reach globally, a press release explains. The company also recently collaborated with several organizations to produce a guide called *Managing Myopia: A Clinical Response to the Growing Epidemic*.

Alcon Teases New Contact Lens, Dry Eye Products

The momentum toward daily disposable contact lenses in recent years leaves open an opportunity for innovation in other modalities, Alcon believes, and next year the company will launch a new monthly replacement contact lens called Total30. The lens will use the same water gradient design found in its Dailies Total1 product line; the similar naming is intended to help patients and practitioners see the two lenses as a family with similar design characteristics but different replacement schedules.

The Total30 launch will begin with a spherical lens at an unspecified date next year, with toric and multifocal options to follow within 12 to 18 months.

Alcon announced the forthcoming lens during the SECO 2021 conference.

At the same event, the company described a next-generation version of its iLux device for meibomian gland dysfunction coming in the second half of 2021. The new model, called Systane iLux^2 (pronounced "iLux squared") will include a camera that can perform meibography and demonstrate the results to patients immediately after the procedure. Alcon says the device allows high resolution visualization rather than simple magnification. Under the company's "No Reason to Wait" program, practices can purchase the current device on the market and then apply that cost to the next-gen one when it launches later this year. ■

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BY ANDREW S. GURWOOD, OD

DIAGNOSTIC QUIZ

Game Over

An anxious patient presents complaining of recent-onset blurred vision at distance. Are his fears warranted?

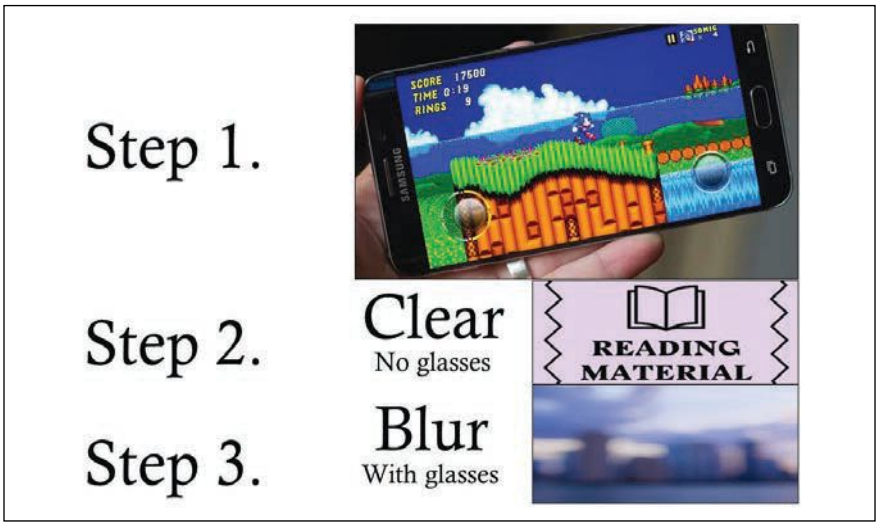
A 55-year-old man reported to the office emergently with a chief complaint of blurry vision at distance in both eyes. He explained in a panic that he had woken up early that morning seeing well, then played a game on his cell phone and noticed that, after he stopped, he no longer needed his reading glasses to read.

He explained further that everything in the distance was blurry. The patient was properly medicated for hypertension and high cholesterol and denied trauma or allergies of any kind.

Diagnostic Data

His best-corrected entering visual acuities were 20/70 at distance and 20/20 at near with a working distance of 10 inches. There was substantial improvement upon the pinhole at distance. External examination was normal for color, brightness and extraocular motilities. Confrontation fields were normal and facial Amsler grid was normal with no afferent pupillary defect.

Refraction uncovered -0.75D sphere, resulting in 20/20 vision at distance. Biomicroscopy showed normal anterior segment structures, and Goldmann applanation tonometry recorded pressures of 16mm Hg in each eye. Dilated exam uncovered normal nerves with no evidence of maculopathy or disc edema.



The patient's description of events: iPhone video play, followed by ability to read without reading glasses but distance vision blur.

Additional Testing

The first important additional test is lensometry. This will permit an understanding of the previous refractive error. It can then be matched against the refraction to understand how things have changed. A detailed history should include whether vision is absent, distorted or blurry, and in which eye and when.

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 94)—Q1: d, Q2: a, Q3: b, Q4: c, Q5: b

NEXT MONTH IN THE MAG

In June, we present our annual retina report. Articles will include:

- The Retina Research Pipeline: Upcoming Advances to Look Forward to
- How to Handle Central Serous Chorioretinopathy
- Be Ready for Acute Retinal Ischemia
- Comanagement Series: Be a Retina Referral Rock Star
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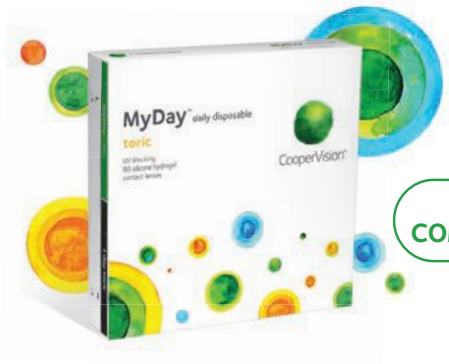

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1. CooperVision data on file 2021. Rx coverage database; 14 to 70 years. **2.** CooperVision data on file, 2017-2019. Based on number of US soft contact lens fits. Includes CooperVision branded and customer-branded equivalent lenses. US industry reports and internal estimates. **3.** Around the clock axis in 10° from Plano to -6.00DS in -0.75DC, 1.25DC and -1.75DC. **4.** CVI data on file 2021. Based on number of prescription options available in the USA across all soft 1-day toric lenses as reported by the 4 main manufacturers and the SKU expansion for MyDay® toric (2H'21). **5.** CooperVision data on file 2020. Kubic masked online survey; n=404 US ODs who prescribe toric soft CLs.

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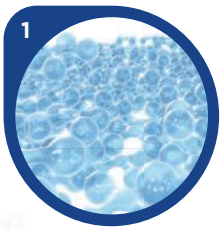

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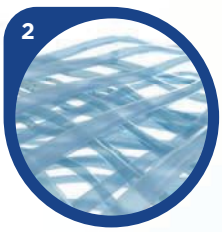

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