REVIEW® of Ophthalmology

October 2019

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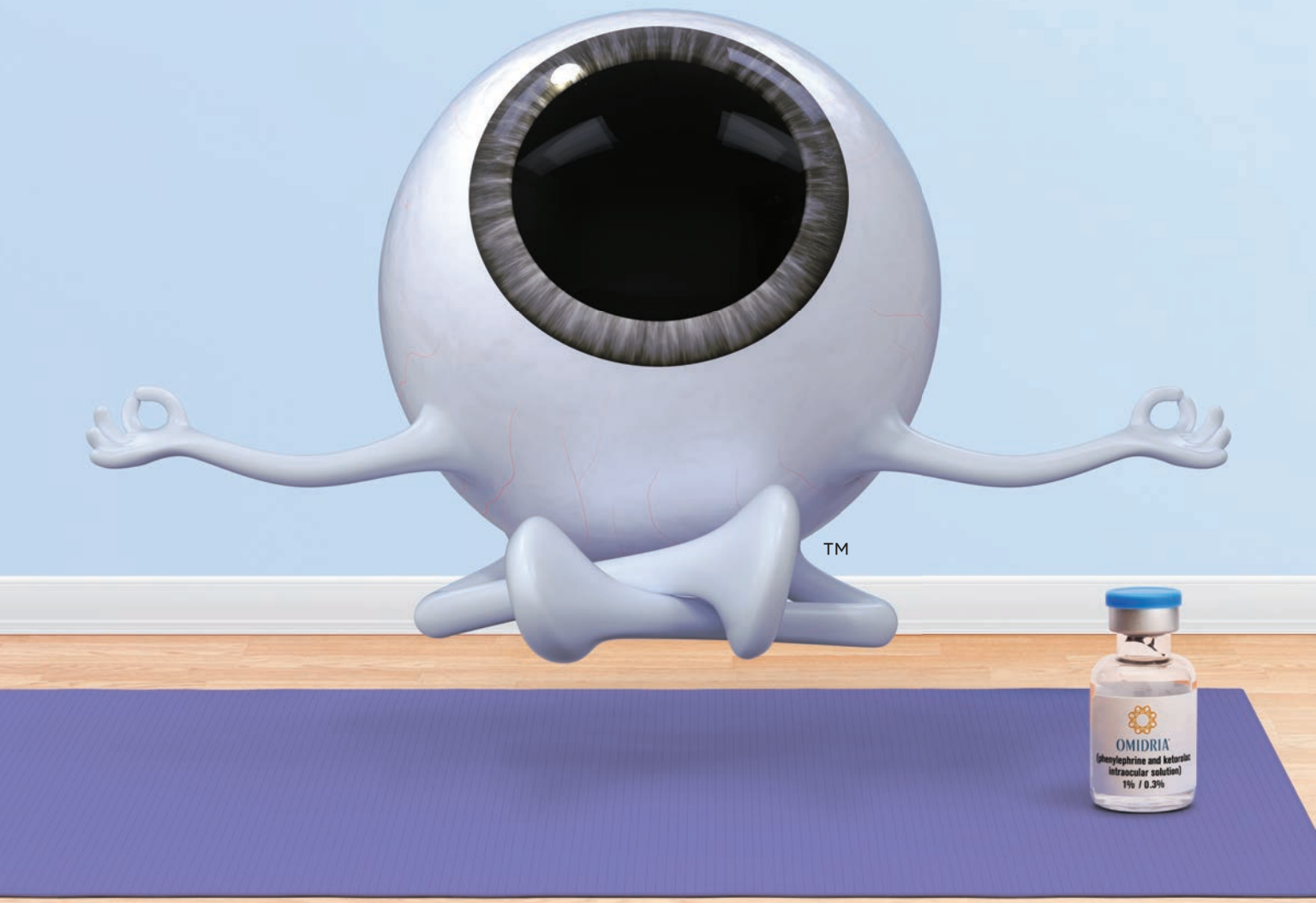
Review of Ophthalmology's 25th Anniversary

A look back at some of the landmark moments that helped shape ophthalmology. P. 46

Less stress, pure success
...in your O.R. day[1]



References: 1. Omeros survey data on file. **2.** Silverstein SM, Rana V, Stephens R, Segars L, Pankratz J, Shivani R, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. *J Cataract Refract Surg.* 2018;44(9):1103-1108. **3.** Rosenberg ED, Nattis AS, Alevi D, et al. Visual outcomes, efficacy, and surgical complications associated with intracameral phenylephrine 1.0%/ketorolac 0.3% administered during cataract surgery. *Clin Ophthalmol.* 2018;12:21-28. **4.** Bucci FA Jr, Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. *Clin Ophthalmol*. 2017;11:1039-1043. **5.** Visco D. Effect of phenylephrine/ketorolac on iris fixation ring use and surgical times in patients at risk of intraoperative miosis. *Clin Ophthalmol.* 2018;12:301-305. **6.** Walter K, Delwadia N, Coben J. Continuous intracameral phenylephrine-ketorolac irrigation for miosis prevention in femtosecond laser-assisted cataract surgery: reduction in surgical time and iris manipulation. *J Cataract Refract Surg*. 2019;45(4):465-469. **7.** Matossian C. Clinical outcomes of phenylephrine/ketorolac vs. epinephrine in cataract surgery in a real-world setting. Presented at: American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. **8.** Al-Hashimi S, Donaldson K, Davidson R, et al. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041. **9.** Gayton JL. E-poster presented at: 15th International Congress on Vision Science and Eye; 2017 Aug 10-11; London, UK. **10.** Katsev DA, Katsev CC, Pinnow J, Lockhart CM. Intracameral ketorolac concentration at the beginning and end of cataract surgery following preoperative topical ketorolac administration. *Clin Ophthalmol.* 2017;11:1897-1901. **11.** Waterbury LD. Alternative drug delivery for patients undergoing cataract surgery as demonstrated in a canine model. *J Ocul Pharmacol Ther*. 2018;34:154-160. **12.** Visco D, et al. Study to evaluate patient outcomes following cataract surgery when using OMIDRIA with postoperative topical NSAID administration versus a standard regimen of postoperative topical NSAIDs and steroids. Presented at: 28th Annual Meeting of the American College of Eye Surgeons (ACES), the American Board of Eye Surgery (ABES), and the Society for Excellence in Eyecare (SEE), Caribbean Eye Meeting; February 1-5, 2019; Cancún, Mexico. **13.** Kauffman L, Walter K, Hess J. Rate of pseudophakic cystoid macular edema using intra-operative and topical NSAIDs alone without steroids. Presented at: ASCRS-ASOA Annual Meeting; May 7-9, 2019; San Diego, CA. **14.** Data on file. **15.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

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OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

The data are compelling and consistent—OMIDRIA makes cataract surgery better for you and your patients

Published and presented clinical studies and manuscripts in press and/or in preparation report that in post-launch (i.e., not included in current labeling), prospective and retrospective, double-masked and open-label, cohort and case-controlled, single- and multi-center analyses, the use of OMIDRIA, compared to the surgeons' standard of care, statistically significantly:

- Prevents Intraoperative Floppy Iris Syndrome (IFIS)[2]
- Reduces complication rates (epinephrine comparator)[3]
- Decreases use of pupil-expanding devices (epinephrine comparator)[3-8]
- Reduces surgical times (epinephrine comparator)[3,5,7,8]
- Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)[6,9]
- Improves uncorrected visual acuity on day after surgery (epinephrine comparator)[3]
- Delivers NSAID to the anterior chamber and related structures better than routine preoperative topical drug administration, resulting in effectively complete postoperative inhibition of COX-1 and COX-2[10,11]
- Decreases the incidence of CME, rebound iritis, and pain/photophobia when used with a post-op NSAID only (no steroid) compared to post-op steroids +/- NSAIDs (no OMIDRIA)[12,13]
- Reduces the need for opioids (i.e., fentanyl) during cataract surgery while decreasing pain scores[14]

OMIDRIA inhibits the release of inflammation-causing prostaglandins, preventing miosis and reducing postoperative pain[15]

OMIDRIA is separately reimbursed under Medicare Part B and by many Medicare Advantage and commercial payers.*
Contact your OMIDRIA representative today or visit omidria.com to learn more.

*Based on currently available information and subject to change without notice. Individual plan coverage, policies, and procedures may vary and should be confirmed. Omeros does not guarantee coverage or payment.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

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

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

OMIDRIA®
(phenylephrine and ketorolac intraocular solution)
1% / 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: *Animal Data.* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

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

Pediatric Use: Safety and effectiveness of LOTEMAX® SM in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

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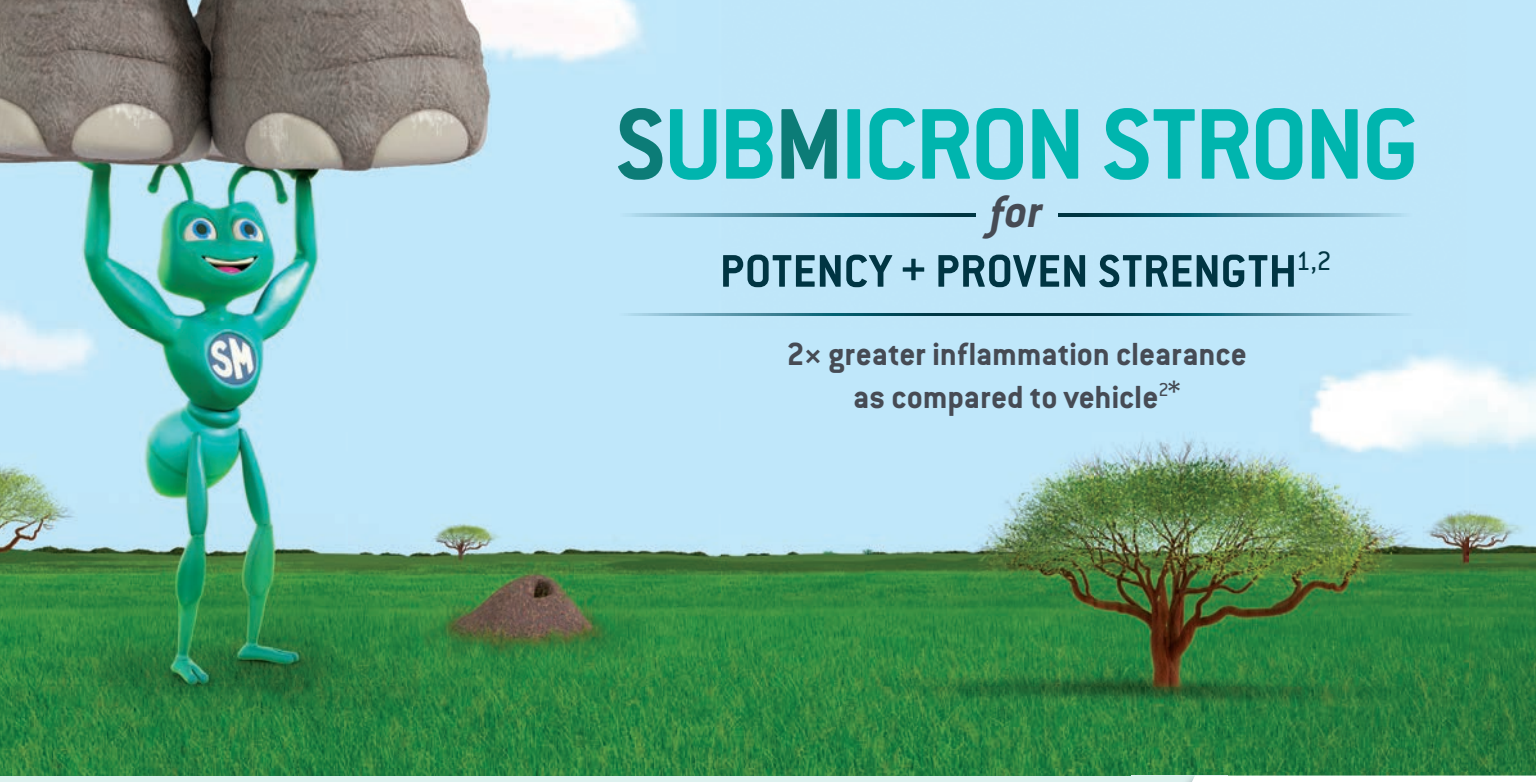
Based on 9669600-9669700 Revised: 02/2019



SUBMICRON STRONG

for

POTENCY + PROVEN STRENGTH[1,2]

2× greater inflammation clearance as compared to vehicle[2]*

SM TECHNOLOGY™

- **Engineered with SM Technology™ for efficient penetration at a low BAK level (0.003%)[1,3]**
- **~2× greater penetration** to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[3]

Clinical significance of these preclinical data has not been established.

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

SMALL & MIGHTY
SUBMICRON PARTICLES

*PROVEN STRENGTH

- **30% of LOTEMAX® SM patients had complete ACC resolution** vs vehicle (15%) at Day 8 (N=371, *P*<0.0001)[1,2†]
- **74% of LOTEMAX® SM patients were completely pain-free** vs vehicle (49%) at Day 8 (N=371, *P*<0.0001)[1,2‡]

†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

‡Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); *P*<0.05 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections.
- Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **2.** Data on file. Bausch & Lomb Incorporated. **3.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019;35(5):291-300.

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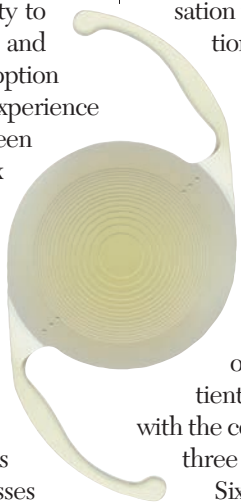
LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

REVIEW NEWS
Volume XXVI • No. 10 • October 2019

Newly Approved PanOptix IOL Sparks Patient Interest

Less than two months after FDA approval of Alcon's AcrySof IQ PanOptix Trifocal IOL and AcrySof IQ PanOptix Toric Trifocal IOL on August 27, early users report high adoption rates for the lenses, which demonstrate the ability to correct near, intermediate, and distance vision. A robust adoption rate is consistent with the experience of surgeons who have been implanting the PanOptix in more than 70 countries since 2015.



"I'm already implanting seven or eight PanOptix IOLs per week," says Elizabeth Yeu, MD, of Virginia Eye Consultants, one of the trial investigators. "The strong possibility that patients will not have to wear glasses anymore is a very attractive option to them."

Surgeons say that it may be simpler to explain the lens to patients, compared to other options in the past.

"With today's other premium lens options, we're used to asking patients if they want a monovision solution for distance and near clarity," says Kerry Solomon, MD, a PanOptix investigator from Mount Pleasant, South Carolina. "If they're not interested in monovision correction, we ask them if they'd like to have their vision for intermediate tasks, such as working on the computer and using cell phones and back-lit items, and use readers for printed material. Would they prefer to make accommodations by using computer glasses? It gets to be a lengthy discussion that, at times, can lead to some confusion. Now we can just ask, "Would you like to be less dependent on glasses for distance, intermediate and near activities? It's an easy conversation to have, and so far, my adoption rate has been terrific."

In an FDA clinical study of 243 patients implanted with either the PanOptix lens or a control lens at 12 U.S. investigational sites, a total of 129 patients (256 eyes) were implanted with the PanOptix (127 in both eyes and two patients in one eye). A total of 114 patients (225 eyes) were implanted with the control lens (111 in both eyes, three in one eye).

Six months after implantation, according to the study, the average best corrected distance vision in one eye was approximately 20/20 for each study group. For intermediate distance, the vision in one eye with the PanOptix lens was approximately 20/25 compared to 20/40 for the control group. The vision for near distance correction with the PanOptix lens was approximately 20/25, compared to 20/63 for the control group. Overall, there were no safety concerns during the study, the company says.

The PanOptix trifocal IOLs are made of same material that was used to create the AcrySof ReSTOR IQ IOL, which has been implanted in more than 120 million eyes globally. The toric PanOptix models were designed by placing new trifocal features on parent ReSTOR Toric IQ IOLs. Alcon officials say the PanOptix intraocular lens has unique properties made possible by the company's new Enlighten Optical Technology, which establishes three focal points: one at near (16 inches); a second at intermediate (24 inches); and a third that redirects light energy for improved distance vision.

The technology allows 88 percent total light utilization at a 3-mm pupil size, reducing dependence on pupil size in varied lighting conditions. A 4.5-mm diffractive zone divides incoming light to create the effective intermediate and near add powers. The anterior surface is designed with negative spherical aberration to compensate for the positive spherical aberration of the cornea. The posterior surface of the optic of the AcrySof IQ PanOptix Trifocal Toric IOL is marked with six indentations (three on either side) on the flatter meridian of the optic. Below are the corrective parameters of both lens types:

- Spherical powers: 6 to 30 D in 0.5-D increments; 31 to 34 D in 1-D increments.
- Add powers: 2.17-D intermediate and a +3.25-D add power at the intraocular lens plane, representing approximately +1.65 D and +2.35 D at the corneal plane after implantation, respectively, for the average eye.
- Cylinder powers (for four toric designs): 1.5, 2.25, 3 and 3.75 D.

In one patient-reported outcome measure, 80.5 percent of study

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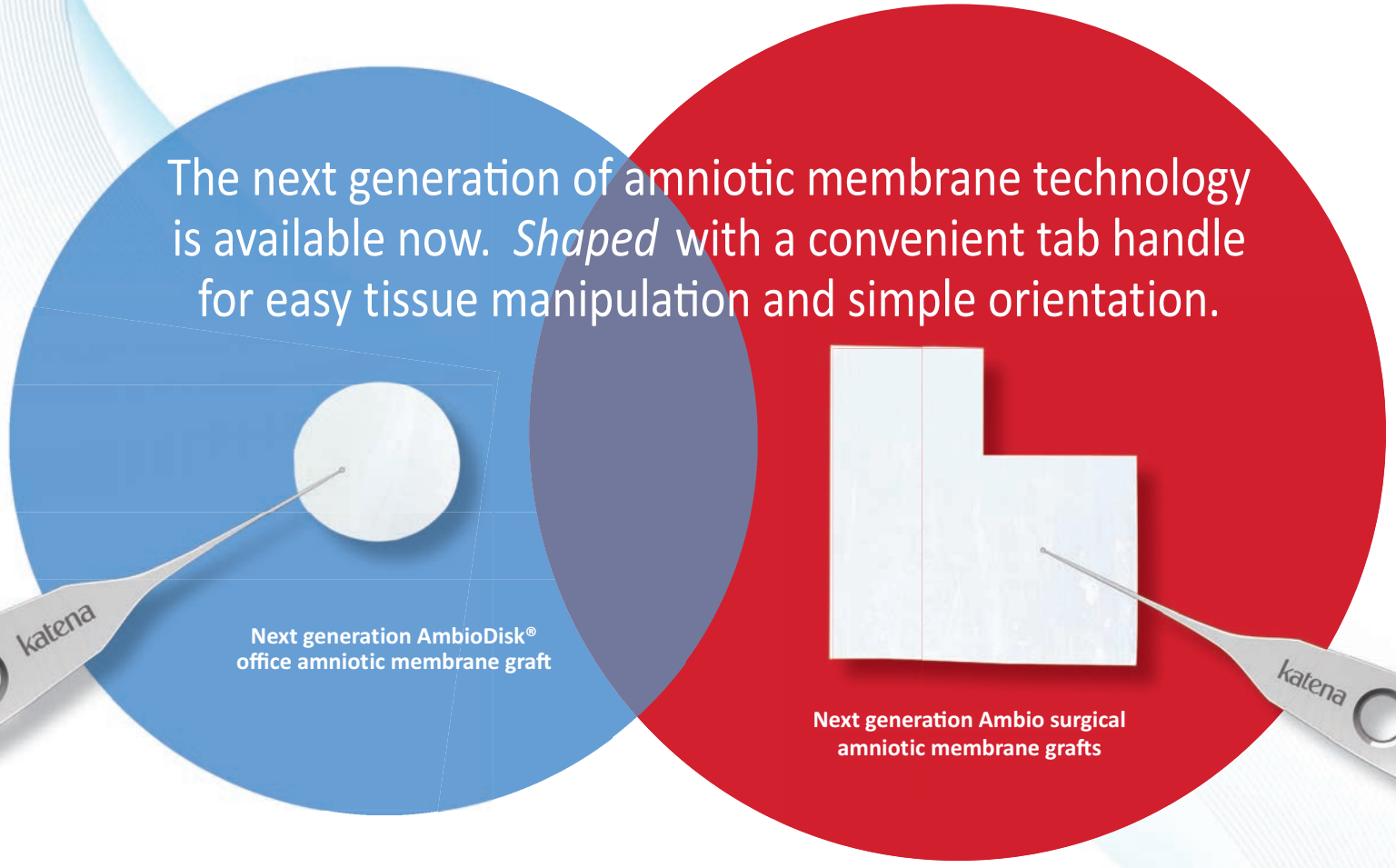

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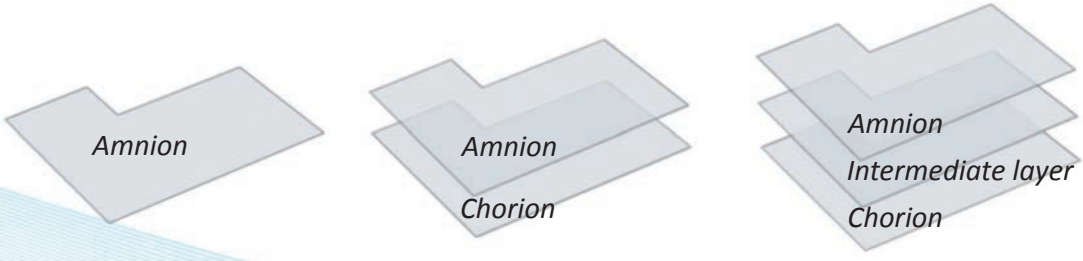

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REVIEW of Ophthalmology

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REVIEW News

Corrections

In "Diagnosing Ocular Surface Disease" in the September issue, the link to the video of Elizabeth Yeu, MD, performing meibomian gland expression had an error. The correct link is vimeo.com/355159648.

In the same issue, on pg. 14 of Technology Update, Dr. Filomena Ribeiro's name was misspelled in the attribution of a chart. *Review* regrets the errors.

participants (99 of 123) who had the PanOptix implanted said they "never" had to wear glasses during the previous seven days.

Alcon notes that the PanOptix can potentially create visual disturbances at night that can be worse than those created by monofocal IOLs. Potential disturbances include glare, rings around lights, starbursts and reduced contrast sensitivity (especially in dim lighting). In the study, for example, 45.2 percent of PanOptix patients were bothered by glare vs. 30.6 percent of the monofocal patients, and 48.8 percent of PanOptix patients were bothered by halos vs. 16.4 percent of the monofocal patients. These side effects may make it more difficult to see while driving at night or completing tasks in low lighting conditions, according to the company.

Alcon plans to begin training U.S. ophthalmologists and making inventory of PanOptix and PanOptix Toric IOLs available through the rest of 2019 into early 2020.

One topic of great interest will be which patients are good candidates for these IOLs. "You need to use the PanOptix on patients with healthy corneas," says Dr. Solomon. "You want to make sure the astigmatism is regular, not irregular. No basement membrane dystrophy or any significant dry eye. You want to treat that first. A healthy ocular anatomy and healthy retina is required. We should be looking at patients with generally healthy eyes who are interested in being less dependent on glasses."

One group of patients was purposely excluded from the FDA trial—those who had undergone refractive surgery. "Speaking to some of my European colleagues, it's not quite clear yet how this lens performs in that setting," says Dr. Solomon. "But I think we'll learn more in the very near future as more discussion about this lens and that topic ensues."

A Major Advance in Transplants

On July 25, Kohji Nishida, MD, and his team at Osaka University performed the first human corneal transplant using sheets of corneal epithelial tissue made from induced pluripotent stem cells. The new treatment gained approval from Japan's health ministry in March, and a woman in her 40s suffering from limbal stem cell deficiency was the first to receive the treatment. At a one-month follow-up, her cornea remained clear.

Corneal diseases are the most common cause of vision loss globally,[1] and corneal transplants are among the transplant procedures in highest demand.[1] There's a significant shortage of donor corneas, however, with only one cornea available for every 70 needed.[2]

Lab-engineered corneas may help narrow this gap. Induced pluripotent stem cells have a high differentiation potential and can proliferate

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(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

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C9048 effective now.
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DEXTENZA IS AN ADVANCEMENT IN STEROID TREATMENT

- Designed to deliver a tapered dose[1]
- Contains fluorescein for visualization[2]
- No additional components or assembly required[2]
- Resorbable, so no need for removal[2]
- Insert can be removed via saline irrigation or manual expression, if necessary[2]
- Physicians rated DEXTENZA as easy to insert[3,4]*

VISIT BOOTH 2323 AT AAO 2019

INDICATION

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

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

*73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3 rated DEXTENZA as easy to insert.

References: 1. Sawhney AS et al, inventors; Incept LLC, assignee. US patent 8,409,606 B2. April 2, 2013. **2.** DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2019. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11. **4.** Tyson SL et al. *J Cataract Refract Surg.* 2019;45(2):204-212.

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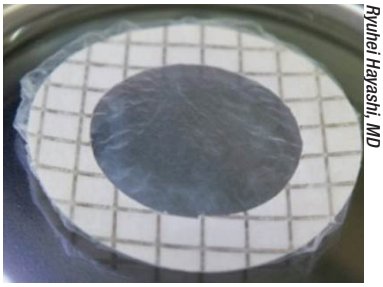

Ryuhei Hayashi, MD

Figure 2. An induced pluripotent stem cell-derived corneal epithelial cell sheet.[4]

indefinitely, making them a potentially unlimited source of transplantable cells.[3]

Last year, Dr. Nishida participated in a study on differentiating human induced pluripotent stem cells into distinct ocular lineages. The researchers used five different isoforms of laminin, a basement membrane protein, as a substrate for the cell cultures and found that distinct laminin isoforms determined selective differentiation of human iPSCs into eye-like tissues, including neural crest and retinal cells.

Ryuhei Hayashi, PhD, one of the study's authors, explains that the binding affinity of laminin and integrins determines the characteristics of hiPSC colonies. "On LN332E8, which has a moderate binding affinity, YAP protein, a sensor for mechanical stress, remained in the nuclei throughout the colony. The presence of YAP promotes corneal epithelial differentiation from human induced pluripotent stem cells. The resulting cell sheets expressed major corneal epithelial markers such as PAX6 and keratin12."

The researchers report that culturing hiPSCs on LN332E8 eliminates the need to pipette away non-epithelial-like cells for corneal epithelial cell sheet production, which was necessary for a previously-attempted method.[4] The researchers also observed that their new laminin differentiation method shortens the culture period.[5]

Embryonic stem cells and mesenchymal stem cells are alternatives, but these have faced clinical hurdles from the ethical debate surrounding embryonic stem cells and the challenges of immunosuppression for donor tissue. Donor iPSCs were used by Dr. Nishida's team for the patient suffering from limbal stem cell deficiency, but iPSCs also have the potential for autologous transplantation, since these stem cells can be obtained from the patient herself with no immune rejection risk.[3]

Four more transplant procedures have been approved by the health ministry, and iPSC therapy may be ready for clinical use in five years. REVIEW

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3. Zhu J, Slevin M, Guo B, Zhu S. Induced pluripotent stem cells as a potential therapeutic source for corneal epithelial stem cells. Int J Ophthalmol 2018;11:12:2004-2010.
4. Hayashi R, et al. Coordinated ocular development from human iPS cells and recovery of corneal function. Nature 2016;531:376-380.
5. Shibata S, Hayashi R, Nishida K, et al. Selective laminin-directed differentiation of human induced pluripotent stem cells into distinct ocular lineages. Cell Rep 2018;25:1668-1679.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

PROLENSA (bromfenac opthalmic solution) 0.07%

Rx only
Initial Rx Approval: 1997

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

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

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial 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 clinical practice.

The most commonly reported adverse reactions following use of PROLENSA ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality, and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests. Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

Rx Only

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INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of full Prescribing Information for PROLENSA® on adjacent page.

References: 1. PROLENSA Prescribing Information. **2.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of [14]C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398. **3.** Data on file, Bausch & Lomb Incorporated.

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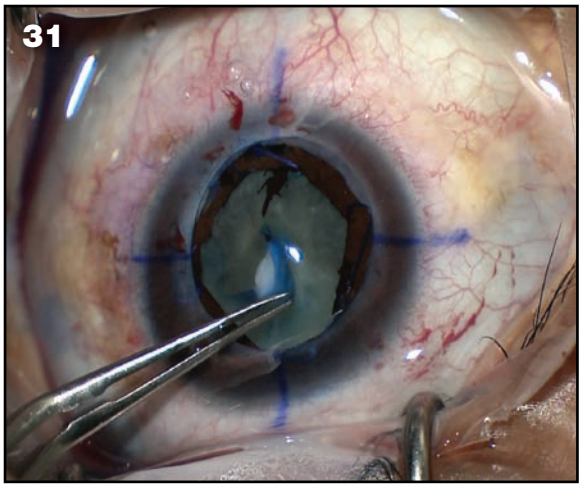

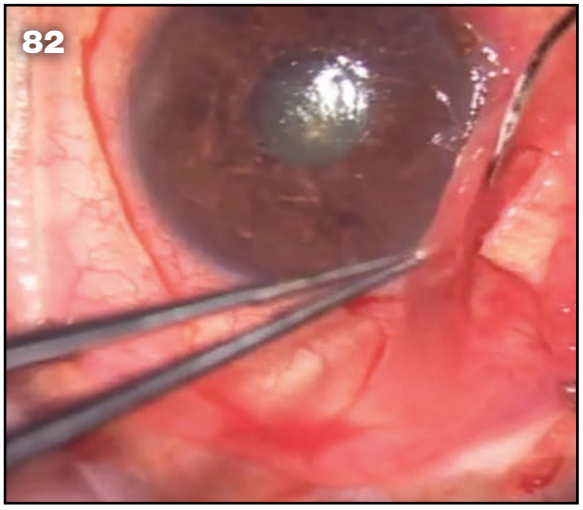

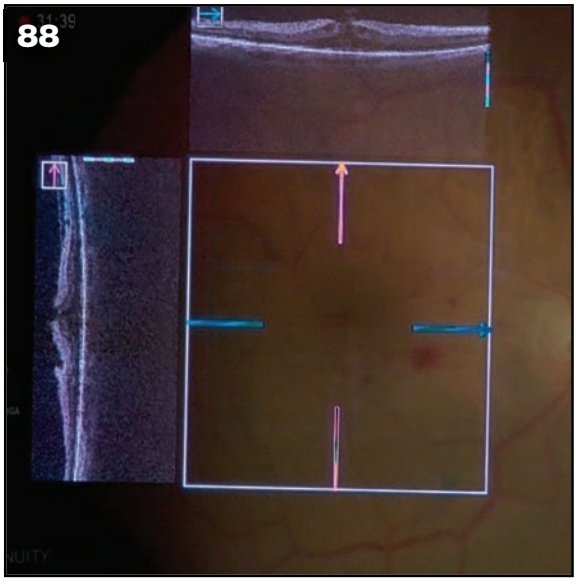

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INDICATION FOR USE. The iStent *inject*® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS.** The iStent *inject* is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

REFERENCE: 1. Samuelson TW, Sarkisian SR, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of an *ab interno* implanted trabecular micro-bypass in primary open-angle glaucoma and cataract. *Ophthalmology.* Jun 2019;126(6):811-821.

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Author: Derek H. Ohlstein, MD

The Importance of Treating Dry Eye Before Cataract Surgery

Derek H. Ohlstein, MD completed his Ophthalmology Residency training at Shands Medical Center at the University of Florida. This was preceded by an Internship in Internal Medicine at the University of Florida. While in residency, he received a broad training in Comprehensive Ophthalmology, with particular emphasis on small incision/sutureless phacoemulsification cataract surgery. Additional areas of interest and expertise include medical retina, glaucoma, and oculoplastics.

Dr. Ohlstein's undergraduate training was at Tulane University in New Orleans, with Bachelors and Masters degrees in Cell and Molecular Biology. He currently practices at Saint Lucie Eye Associates in Florida.

Cataract surgery is very results oriented and with that comes high expectations from patients in terms of outcomes and improvement in vision. Due to this, we tend to place much emphasis on pre-operative decisions such as the type of IOL to use. However we need to place equal importance on looking at the ocular surface and meibomian glands to detect any possible dry eye disease and address this prior to surgery in order to avoid inaccurate pre-surgical lens calculations, sub-optimal lens choices, and compromised outcomes.

The Role of the Tear Film

In our practice about 70% of patients have some form of dry eye, with at least 50% being moderate to severe. In many cases of dry eye the tear film is deficient, and if this is not addressed prior to surgery, the patient most likely will have more blurred vision and glare. Particularly with premium or advanced lens patients, we want to make sure we do everything possible to produce good results quickly. When I initially see patients for cataract surgery, I always do a dry eye evaluation, which includes looking at the meiobomian glands, and conducting an osmolarity test and a tear breakup time (TBUT) test.

> *"we need to place equal importance in maximizing the fidelity of these calculations by examining the ocular surface for meibomian gland dysfunction and dry eye disease"*

If a patient is diagnosed with dry eye disease, the next step is to determine the best treatment option. Many patients use artificial tears, but these only address their symptoms not the root cause of their dry eye. If a patient's tear film is deficient, there are options such as warm compresses and also prescription medications such as cyclosporine, lifitegrast, or an antibiotic. However these

treatments don't treat the root cause and can also take months to see meaningful improvement in the tear film. This can delay the patient's surgery, leading to unsatisfied patients and practice disruptions.

Treating the Root Cause

I recently started using the NuLids System, a doctor directed, at home treatment for patients with dry eye. NuLids effectively alleviates symptoms by stimulating and rejuvenating the meibomian glands back to a healthy state. NuLids is safe and clinically effective, and in addition to treating dry eye is good for ocular hygiene, Blepharitis and Demodex. Studies demonstrated a 65% improvement in tear film breakup time (TBUT) and an 81% increase in Meibomian Gland Yielding Liquid Secretions in less than 30 days with NuLids.[1] Additionally, NuLids has been shown to remove scurf, improve Meibomian Gland effectiveness, and increase Meibomian Gland output by 2 times.[1]

With daily use, our patients typically see a noticeable difference within one to two weeks of using the device, with improved TBUT, markedly less capping of the meibomian glands, and reduced inflammation from Blepharitis. NuLids is quick and easy to use and only takes about 15 seconds per lid each day. It's also cost-effective for patients.

A Game Changer for Cataract Patients

We have seen patients with irregular IOL calculations who return after using NuLids for just a few weeks and we get good measurements and lens calculations in preparation for cataract surgery. In fact we haven't had a patient yet where we didn't get coherent lens calculations after using NuLids. Additionally when repeating topography for phaco measurements, there are less artifacts associated with dysfunctional tear films.

"We are getting cleaner lens calculations"

One example is a recent cataract patient who wanted a Technis Symfony® lens (Abbott). At her pre-opertive appointment her left eye topograhy was 3 D of cyl and the IOL master only read 0.5 D. Since the basic lens formula is P = A – 0.9 K – 2.5 AL, this could have resulted in a 2.5 D of error in lens choice. We repeated the measurements, and had similar unreliable readings. She was already on Restasis and artificial tears. She needed the phaco performed in a narrow window of time, so we started warm compresses and the Nulids System. One week later we repeated calculations and all the measurements were within 0.25 diopter of cyl. with POD#1 20/20 vision.

The NuLids System has truly been a game changer for our practice. We are getting cleaner lens calculations, so there is less chance of being off on astigmatism measurements and a better chance of getting good lens calculations the first time. We are also getting a better view through the cornea during surgery, which makes it easier and our calculations cleaner. Ultimately this all leads to better patient outcomes and satisfaction.

References:

[1] Olkowski, J Use of a personal at-home mechanical eyelid cleaning device for the treatment of dry eye disease, blepharitis and meibomian gland disease. ASCRS ASOA Abstract, Los Angeles, CA, 2016

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EHR: Making the Most of Patient Portals

This feature of most electronic health record software packages can benefit patients and practices alike—if used effectively.

Christopher Kent, Senior Editor

For many ophthalmologists, moving from paper to electronic health records has been a challenging (many would say painful) necessity, done primarily to avoid government penalties. But now that EHR has become a more familiar part of most practices, many doctors are devoting attention to maximizing its benefits.

One feature that's always offered potential benefits for both a practice and its patients is the so-called patient portal, a secure digital channel allowing patients to communicate directly with the practice via a computer or smartphone. "A patient portal is all about connectivity between the doctor and the patient," says Sara B. Rapuano, MBA, an ophthalmology practice management consultant based in Philadelphia. "HIPAA rules state that we shouldn't use public email to communicate with patients about their health issues; the patient portal gives us an alternative, secure way to do that. In addition to letting patients talk to the doctor, it can also be used for appointment reminders, paying bills and so forth."

Here, individuals who have worked extensively with patient portals share what they've learned about their benefits and pitfalls, and offer advice for making the most of yours.

The Evolution of Portals

Not surprisingly, using EHR to communicate with patients wasn't most practices' main focus when initially switching away from paper records. "At first, the big government push was just to get everyone using electronic health records," notes Ms. Rapuano. "At that point we were all trying to get our patient data into electronic form and arranging to send in prescriptions electronically, things like that, so that we could comply with the regulations. It wasn't clear that it was improving patient care; it was more about checking off a box for the quality program requirements. A lot of doctors referred to this as 'meaningless use.' "

The government's initial ideas about how patient portals should be implemented were also met with resistance. "At the outset," she says, "the government said, 'You have to have the portal turned on and you have to get 15 percent of your patients to sign up for it.' So when patients came into the office, we'd invite them to sign up for access to the portal. However, that turned out to be a challenge, because many patients simply weren't interested. Many elderly patients don't even have a computer, and if they do, they might not be good at remembering passwords or following instructions.

"As a result," she continues, "many ophthalmologists got upset and said, 'This isn't fair; we have no control over whether or not our patients do this.' Eventually, the government relented; now, they just say you have to have the EHR functionality and prove that it's working." (She notes that she hasn't seen the 2020 regulations, which could conceivably involve changes to this situation.)

Meanwhile, EHR systems have steadily improved, while doctors and practices have gradually become accustomed to using them. "Today's patient portals are far better than the ones we had when my practice started using EHR 10 years ago," says Ellen Adams, MBA, director of compliance at Ophthalmic Consultants of Boston. "I signed up to use the portal as a patient when we first switched to EHR,

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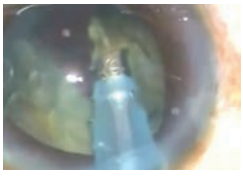
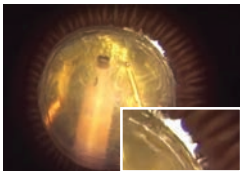
Traditional Lens cracking

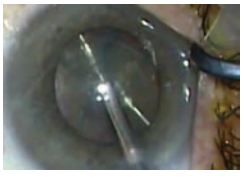


Lens cracking

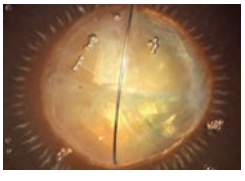


Broken zonules

Lens fragmentation with ZEISS miLOOP



Lens fragmentation



Preserved zonules

[1]without the need to apply energy from phacoemulsification

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Most patients below age 75 are accustomed to using electronic devices to communicate, and they'll be happy to use your patient portal—if you can show them that they'll benefit from using it.

partly so I could see what our other patients would be experiencing.

"The early version of the portal was incredibly frustrating and clunky," she says. "Most of our early-adopter patients eventually dropped out, and I know it's because the portal didn't work well. I could see that some of the functionality we wanted was being interrupted by security concerns. For example, I couldn't just say, 'Please mark that entry in my record as incorrect.' In contrast, the newer patient portals will let the patient put a mark on the record and say, 'Please correct this.' "

Benefits of a Patient Portal

Some benefits of using a patient portal to communicate with patients are easy to see—security and privacy among them. But there are other reasons to employ a digital communications channel:

• ***Younger patients like communicating this way.*** "Patients who spend much of their day using smartphones and computers understand this technology and love using it," notes Ms. Rapuano. "They want to be able to get a refill on a prescription without having to sit down, dial the phone, talk to a human, wait for a callback and then deal with it. They'd much rather send you a note through the portal. On the other hand, older patients usually prefer talking to someone on the phone. As a patient, I log in and look at what's in my own portal on a regular basis, but my mother doesn't. So use of the portal seems to be age-specific."

• ***You can respond to patient messages all at once, at your convenience.*** "If you're a doctor who likes to answer all of your calls so you don't get a stack of messages in the morning, you'll like having a patient portal," Ms. Rapuano says.

• ***A portal reduces the number of phone calls at the front desk.*** If patients are able to manage their concerns without calling, your staff will spend less time answering phones and more time focusing on other tasks.

• ***Interactions are documented, helping to prevent malpractice claims.*** "When you communicate through a patient portal, it's creating a digital record of that interaction," notes Ms. Rapuano. "From a malpractice standpoint, that's really helpful. If my patient sends a secure message telling me that he's having some distress, my reply that I want him to be seen as soon as possible is documented. If the patient doesn't show up and ends up with a problem, you have documentation that you tried to help him."

• ***Letting patients provide medical history information ahead of time shortens new-patient visits and improves the patient experience.*** "In the old days patients used to get a new-patient packet in the mail with a form to fill out that they'd bring to the office for the initial visit," Ms. Rapuano points out. "Now, if a practice is using a portal effectively—and most EHR systems have the ability to do this—the patient is able to put in insurance information, answer all the demographic questions and even pay the insurance co-pay before showing up at the office. The patient can even explain the reason for the visit: 'I'm coming to you because I saw my general ophthalmologist last week and she thinks I may have keratoconus, and I want to be evaluated for that. She sent you a referral letter.' Having all of tming tohese issues handled before the patient gets to the office can save you a lot of time."

Ms. Rapuano notes that having information input ahead of time by the patient can also improve the patient experience. "In some systems, the answers the patient provides are imported directly into the medical record," she adds. "When we first started using EHR, patients would sit there and watch us entering information into the computer. As a patient experience, that's a real downer. On the other hand, if the patient has already filled out the questionnaire, the technician can just verify that it's correct and get right to addressing the concerns that brought the patient to your office. Your technician can focus on checking vision, taking the pressures, or doing a visual field or an OCT. In

my experience, a patient portal really does improve the patient experience—at least for those patients and practices that embrace it."

Getting Patients Involved

Of course, patient use of an EHR portal is voluntary, and getting patients to come on board isn't always easy. "Back in the days of meaningful use we were told we had to get patients to use the portal," recalls Ms. Adams. "My thought was: 'I'm going to drive home with these 75-year-old patients, get them to log on to a computer and show them how to use this?' It seemed crazy.

"Fortunately, most of our patients under 75 years old are willing to sign up for the portal if we present it to them in the right way," she continues. "With patients 75 or older, computer use has been spotty at best. I think some younger family member gives them a computer but doesn't bother to help them learn to use it, so they don't. The age cutoff makes sense to me, because if you're 75 and you retired about 10 years ago, that's about the time we became fully enmeshed in using computers. Before that, home computers weren't as common."

Ms. Adams points out several factors that will help to motivate patients to use the portal:

• ***Functionality***. Ms. Adams says a key factor in whether patients will use a patient portal is how much value it has for them. "The more functionality you can offer to the patient, the easier it is to get them to participate," she says. "Early on we told patients that the portal would make it easy to change an appointment, get a medication refill or send the doctor a message. However, they could do these things over the phone. We were asking them to remember a complex password and get on the computer to do the same thing.

"Now it's an easier sell," she says. "We can say to patients: 'You can make an appointment; you can refill your medications; you can pay your bills online; you can review your chart; you can check your appointment schedule; and you can communicate with your doctor electronically.' The point is that it's important to provide as much functionality as possible if you want to motivate patients to actually use the portal."

• ***Round-the-clock accessibility.*** Another key selling point is that the portal is open 24/7. "That's a significant advantage for most patients," Ms. Adams says. "The patient can take care of things when it's convenient for him or her, like in the evening or on the weekend when our phones are on service. So we like to sell the portal as a convenience: 'When you're thinking of something and we're not available, use the portal.' If you point out that this system lets them interact with us on their time schedule, they more readily adopt the technology."

• ***No unnecessary office visits.*** Ms. Adams points out that the patient portal allows patients to ask basic questions without having to come into the office. "Here in Boston patients pay $48 or more just to park their car," she notes. "Patients are unhappy before they even walk through the door! So our doctors and patients like being able to address non-urgent issues through the portal.

"I love using the portal for the same reason," she adds. "It may save me a visit. Instead of having to go into the office I can get on the portal and ask a question about a symptom. If it's serious, they let me know. If not, I've saved myself a trip to the office. Depending on the demographic, that's a great selling point."

Like any other tool, patient portals come with potential pitfalls. The following strategies can help your practice create a good experience when using your portal—for your doctors, patients and staff.

The Patient's Perspective: Dealing With Multiple Portals

Ellen Adams, MBA, director of compliance at Ophthalmic Consultants of Boston, notes that a big problem with patient portals is patients having to deal with different portals for different doctors. "I was talking to a patient today, suggesting that she go into her portal to see her medication list and suggest revisions to it electronically," she says. "The patient said, 'I already have two portals. There's no way I'm going to add a third.' I don't blame her. Today, patients usually have a different portal for every provider. In fact, this patient's primary provider uses Epic, just as we do, but the Epic portal for her primary care provider is different from the Epic portal for our practice.

"How can we get people to use a patient portal when one provider is on one system and the next group is on a different system, or they're on the same system, but they don't talk to each other?" she asks. "I foresee this being one of the big problems we're going to have to resolve moving forward. Patients will drop out just because they're sick of having to use multiple complex passwords. If it's health-care information, you can't just use your dog's name as your password."

Sara B. Rapuano, MBA, an ophthalmology practice management consultant based in Philadelphia, notes that when an EHR is in widespread use, this problem can sometimes be resolved by linking multiple accounts that are attached to the same software. "Epic is one of the most widely-used EHRs in the United States," she notes. "As a patient I've seen doctors at two different health-care systems that both use Epic. When I connected to the second system's portal it asked me if I wanted to link my two accounts so doctors at both locations could see each others' records. Of course I said yes. I've also observed that some of the most popular systems are willing to share files with each other, although that doesn't necessarily involve the patient portal."

A few companies, among them Healthjump in Philadelphia, are trying to create a solution to the problem of patients managing multiple portals. Healthjump, for example, assembles and normalizes data from different EHR and practice management systems. This allows practices to build a personal health record that lets patients see their aggregated health data (from multiple sources) all in one place. Jose Horta, director of product at Healthjump, says that the Healthjump system is used by an array of health-care systems that encompass multiple doctors and practices using different EHRs, as well as technology vendors whose customer base uses a wide array of EHR and practice management systems. (Healthjump is currently able to connect to more than 40 different EHR and practice management systems for this purpose, and is used in more than 400 practices nationwide.)

—CK

Strategy 1: Triage Messages

"When I told our doctors we were going to have to get patients signed up to use the portal, they panicked," says Ms. Adams. "They were already overwhelmed with their communication responsibilities, and most of the incoming portal messages were about things the providers didn't need to see, such as changing appointments, asking to refill their medications, paying bills or sometimes asking random questions. The vendor suggested funneling the incoming messages to staff members who could triage them.

"Now, the people who answer our phones are the first ones to see the messages that come in," she says. "They distribute them appropriately. For example, our central scheduling group monitors the queue and pulls off all of the questions about appointments. Those messages never go past that group. And we have a subspecialty team within our scheduling group that manages medication refill requests; they go down a checklist to decide how to handle them. They check to see whether the patient has been coming in for appointments. If not, the request goes to somebody else to triage. If the patient has kept her appointments, there's a follow-up appointment scheduled and the medication is something the doctor said to take, they send the refill request to the doctor's queue with a note that states this and asks the doctor to sign off, if appropriate. The doctor can quickly review and send the medication request in. This system works very well; we have zero complaints about portal medication refills now.

"Finally, if a message does have to be seen by a doctor, it goes to the doctor through somebody else who reviews it for relevancy," she says. "That person will add comments about whether or not any action has been taken so the doctor has a complete package to respond to. A few patients are kind of abusive, sending messages constantly; but again, staff members manage them, so the doctors aren't being bothered. We find this preferable to having those patients calling the office constantly."

"It's very rare that a provider gets a message directly, bypassing our system," she adds. "That only happens when the provider initiates the conversation string."

Strategy 2: Activate Gradually

"In many systems, you get to configure your preferences," Ms. Rapuano explains. "In fact, just because you have a system like NextGen, that doesn't mean the patient portal is turned on. You have to set it up, which includes deciding what functions you want to enable at the current time. Then, you also have to configure how

each function will work. For example, incoming messages might be configured to go to one or two individuals who can redirect them to an appropriate doctor or staff member, based on content, mimicking the controls you might currently have for a phone triage."

Ms. Adams says it's important to activate your portal's capabilities one at a time. "Getting a portal and turning on everything at once could be overwhelming," she says. "We activated ours in steps. We started by giving patients an email option. When messages started coming in, we saw that the vast majority were questions about appointments. So, we activated the appointment function next. That option makes it easier for patients to set up or change an appointment, and any messages about appointments were moved into the appointment module at our end. Interestingly, activating this made no difference to our work load, because the messages coming in were essentially the same; it's just that they came in via this bucket instead of that bucket.

"Next, we activated our medication refill request capability, because we could see that was the number two thing patients were using the portal for," she continues. "Of course, patients could ask about this in an email, but turning on this option simplified the process for both the patient and our staff.

"The most recent thing we've turned on was the payment option, which allows patients to pay their bills electronically," she says. "Patients are very happy about that. The week it went live I thought we should let patients know about the new feature, but by the time I suggested this, payments were already coming in. In fact, we probably would have turned that on earlier, because when people call about billing they want to use their credit card, and managing this manually over the phone is a nightmare. However, there were issues with turning it on because we're integrated into a larger medical system."

Ms. Adams says the next thing she hopes to get turned on is patient forms. "This allows new patients to fill out paperwork before they come in to the office," she says. "The patient doesn't have to sit there in the waiting room balancing a clipboard on her knee filling out a piece of paper. It's much easier for everybody."

She points out that turning on the email option first makes a lot of sense, because patients for a given practice might be asking for something different than the patients in her practice. "If you're in a glaucoma-heavy practice, most patient questions will probably be about medication refills," she points out. "So that might be the first or second module to turn on. Turning on the email option first will help you get a sense of what patients will want to use the portal for."

Ms. Rapuano agrees. "Patient portals are capable of doing a lot of things, but the workflow in the office has to be ready to handle all of those capabilities," she says. "It's easy to see the possibilities and think, 'Wow, we should do all of this!' But you have to make sure you understand what you're capable of handling in-house. If you activate every option and your staff isn't able to handle it, you'll create a bottleneck."

Ms. Rapuano also notes that it's easy to ignore the patient portal capabilities your EHR may have. "Some practices purchase a Cadillac of a system but drive it like a bicycle," she says. "Most EHR systems can do a lot, and it's important to understand their capabilities. Then, if you decide you want to take advantage of one of those capabilities, someone in your practice has to sit down and map it. For example, if you have a new-patient form, you have to work with your IT people to map that form into the correct part of the EHR."

Strategy 3: Be Email-Proactive

One problem that Ms. Adams reports encountering is that many staff members are young and accustomed to communicating via text and email; they don't appreciate that patient communications need to happen through a secure portal. "The idea that the weakest link in your security is your employees is doubly true when it comes to communicating with patients," she notes.

"Employees often don't understand that if a patient's health information escapes we have a serious problem on our hands," she continues. "We end up with a string of clinical information going back and forth through Google mail that should be in the medical record. It's now lost forever in an email string. Meanwhile, the doctor doesn't know this correspondence took place until the patient gets angry and sends us a printout of the communications with our staff member to prove the case was mishandled.

"Unfortunately, getting staff to switch from email to using the portal can be a real uphill climb," she continues. "Email is easy to use, while using the portal requires opening the medical record. I explain to staff that communicating with patients via email is against our policy, but I can't always tell if staff members are doing it because there's no way to monitor everyone's email."

Ms. Adams notes that staff who do use email to communicate with patients (despite office policy) often end up regretting having done so. "Aside from security and malpractice concerns, I've had several staff members end up with the patients emailing them incessantly," she says. "Eventually they realize they're being abused. So, we have a rule: Don't put your email on your business card. Don't give your patients your email address. And never communicate with patients by email.

"Unfortunately, your staff may be contacted by patients via email even if they haven't given out their email address," she points out. "It's often fairly easy to deduce the email address of anyone in your company. The thing that identifies each staff member's address is often just the first initial and last name of the person, and a patient may figure that out. So our staff members do get uninvited emails from patients, and the temptation is to just reply.

"To help prevent that from happening, we've taught our staff that if they get an uninvited email from a patient, they should reply with a message that looks like an automated reminder," she says. "The reply says, 'I'm not able to communicate via email. Please call the office at xxxxxx, or sign up for the patient portal.' I've scripted the message, so many staff members simply paste it into their reply.

"It's not an ideal solution," she adds, "but it does seem to work."

Additional Pearls

These strategies can also help ensure a positive patient portal experience:

• ***Consider investing in a portal created by a standalone company.*** "Talking to doctors at meetings, I've noted that some doctors are using portals that aren't part of their EHR system," says Ms. Rapuano. "The big EHR companies are at a disadvantage in a way, because they're developing entire software platforms and they have to make sure they keep complying with changing government regulations.

"On the other hand, a small company focused on a single thing, such as a patient portal, may end up creating something you'll find more user-friendly," she says. "Of course, using that option will come with an additional financial cost."

• ***Stay aware of system upgrades.*** "Once you've invested in an EHR system, have someone in your practice monitor upgrades and stay abreast of new system capabilities," says Ms. Rapuano. "More functionality is being added all the time, partly because people ask for new things. Once you've implemented a system you may not want to change anything, but some of the new modifications might really be good for your practice."

• ***Make sure the patient understands what the portal should not be used for.*** "When I log into the University of Pennsylvania portal," notes Ms. Rapuano, "it clearly says, 'Any questions you put in here may not be answered for 24 hours.' It's telling you in bold letters that this portal is not designed to help you in an emergency. Make sure your portal does the same."

It Really Can Work

"I've trained many doctors to use EHRs," notes Ms. Rapuano. "If you embrace electronic records, it can really make your life better.

"However, whether or not it does make things better depends a lot on how the doctor thinks," she points out. "Some doctors will find EHR to be a burden, and you definitely don't want to do something that's going to contribute to burnout. But if you're willing and able to embrace it, functions like the patient portal can both improve the patient experience and make your life a little easier."

"Having a patient portal works really well for us," Ms. Adams adds. "It's good for both our patients and our practice, and our patients are actually using it." REVIEW

Ms. Adams and Ms. Rapuano report no relevant financial ties to any product mentioned. However, Ms. Rapuano notes that her son is an employee at Epic Systems.

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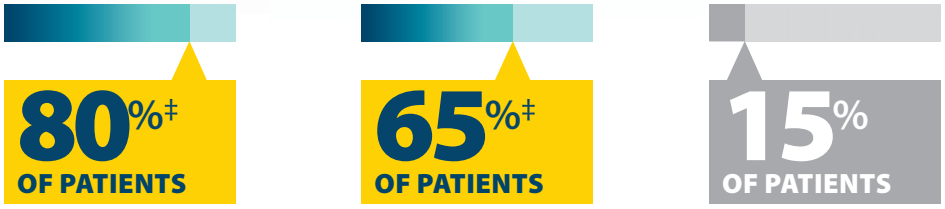
EYLEA® (aflibercept) Injection For Intravitreal Injection

POWER AGAINST

In PANORAMA, EYLEA significantly improved DR severity scores at week 52[1]

Proportion of patients achieving a ≥2-step improvement in ETDRS-DRSS* score from baseline (primary endpoint)[1,†]



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months).[1]

Efficacy and safety data of EYLEA in DR are also derived from VISTA and VIVID.[1] The percentage of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at 100 weeks was 38%, 38%, and 16% in VISTA and 32%, 28%, and 7% in VIVID with EYLEA 2 mg every 8 weeks after 5 initial monthly doses, EYLEA 2 mg every 4 weeks, and control, respectively (secondary endpoint).[1]

PANORAMA study design: Multicenter, double-masked, controlled study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without central-involved DME (CI-DME) (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1) 3 initial monthly EYLEA 2 mg injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; 2) 5 initial monthly EYLEA 2 mg injections, followed by 1 injection every 8 weeks; or 3) sham treatment. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the ETDRS-DRSS from baseline to week 24 in the combined EYLEA groups vs sham and at week 52 in the EYLEA 2 mg every-16-week and EYLEA 2 mg every-8-week groups individually vs sham. A secondary endpoint was the proportion of patients developing the composite endpoint of proliferative DR (PDR) or anterior segment neovascularization.

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control), at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, efficacy endpoints included the mean change from baseline in best-corrected visual acuity (BCVA), as measured by ETDRS letters, at 52 weeks (primary endpoint) and 100 weeks (secondary endpoint).

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA 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.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: An established grading scale for measuring the severity of DR.
†Full analysis set.
§3 initial monthly injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks.
‖5 initial monthly injections, followed by 1 injection every 8 weeks.

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Significantly fewer patients developed PDR or ASNV with EYLEA at week 52[1]

Composite endpoint of patients who developed PDR or ASNV at week 52 (event rates) (secondary endpoint)[1,†]

EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

All patients were treatment-naïve to focal or grid laser photocoagulation, panretinal photocoagulation, and any anti–vascular endothelial growth factor (anti-VEGF) treatment.[2] Composite endpoint of developing PDR or anterior segment neovascularization (ASNV) was diagnosed by either the reading center or investigator through week 52. Event rate was estimated using the Kaplan-Meier method.[1]

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.
- 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.

References: 1. EYLEA® (aflibercept) Injection full Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

05/2019
US-LEA-14375

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.

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How to Deal with A Cloudy Cornea

Clear the way with careful preop planning, surface treatments, adaptive procedures and more.

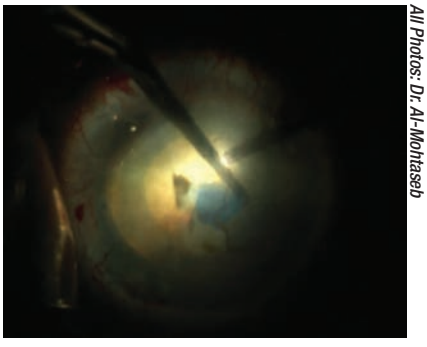
By Mina M. Naguib, MD, and Zaina Al-Mohtaseb, MD, Houston

As you know, careful preoperative planning is essential to succeed with cataract surgery. Whether we're inquiring about the use of blood thinners, assessing a patient's ability to lie flat or identifying anatomical changes such as weak zonules or a shallow anterior chamber, our success relies heavily on finding sources of potential complications before surgery and adjusting our approach as necessary.

One major difficulty is the presence of corneal pathology that causes opacification and hinders a clear view through the cornea to the lens, increasing the likelihood of inaccurate IOL calculations. Common causes of this type of corneal pathology include a central scar, severe corneal surface disease, limbal stem cell deficiency and endothelial cell dysfunction. In this article, we'll address each of these sources of "cloudy" corneas and provide tips to help you confidently respond to the challenges they present.

Optimizing the Ocular Surface

Before performing IOL calculations for a patient with a cloudy cornea, you need to treat ocular surface a disease adequately. This step helps ensure accurate biometry and topography readings, which can change significantly before and after treatment. Additionally, treatment of ocular surface disease not only improves visualization during surgery but also decreases the risks that recalcitrant disease might pose after surgery. Most important, control of OSD will lead to a better overall refractive outcome and higher patient satisfaction.



All Photos: Dr. Al-Mohtaseb

Figure 1. Creation of capsulorhexis using trypan blue and transcorneal illumination with a light pipe.

Keratometry is essential to mapping out a good approach to these patients. Looking at the placido rings helps to diagnose subtle cases of epithelial basement membrane disease, for example. If necessary, perform epithelial debridement or excimer laser phototherapeutic keratectomy at least three months before obtaining final IOL calculations for these patients.[1] Failure to identify the presence of EBMD will lead to inaccurate IOL selection and dissatisfied patients with poor visual outcomes.

Less common but more serious conditions that can lead to poor visualization include Stevens-Johnson syndrome[2] and graft-versus-host disease. Preoperative preventative and stabilizing measures are the keys to achieving satisfactory visual outcomes in these cases. In both SJS and graft-versus-host, inflammation leads to changes, predisposing patients to severe dryness, conjunctival compromise, deficient tear production and eyelid margin disease. Because surgical manipulation can exacerbate the disease process, you must aggressively control any surface disease or existing inflammation.

Treatments to Consider

Consider a broad armamentarium when preparing the ocular surface

for surgery. You can try frequent use of preservative-free artificial tears, topical corticosteroids, topical 0.05% cyclosporine (Restasis, Allergan) or 0.5% lifitegrast (Xiidra, Shire) and/or serum tears.

These treatments may not be enough, however, and the use of amniotic membrane grafting, bandage contact lenses, tarsorraphy or the PROSE (prosthetic replacement of the ocular surface ecosystem) Lens (BostonSight) may be useful in severe cases, both before and after surgery.

Patients with a history of ocular herpes simplex or herpes zoster infection should be carefully educated about the increased chance of disease reactivation.[3]

In general, patients should not have evidence of active infection for at least three months before surgery.[4] No clear guidelines exist for antiviral prophylaxis. However, for patients who aren't already receiving treatment, consider starting them on prophylactic dosing (depending on the type of previous infection) for at least one week before surgery. Continue this therapy for up to six months after surgery, until discontinuing topical steroids.

Besides employing these strategies, you may need to attempt limbal stem cell transplantation to optimize the surface and the view through the cornea before surgery in cases of limbal stem cell deficiency and severe corneal conjunctivalization.

Preoperative Planning

Once control of preexisting pathologies is optimized to the greatest degree possible, visualization through a cloudy cornea should improve and can be maximized with specific surgical strategies.

As with all cataract surgeries, proper lens selection is the key to achieving a good outcome. However, corneal opacities that persist even after the surface has been optimized can prevent accurate biometry readings, although this is true to a lesser extent with newer optical biometry systems. If you're concerned that biometry findings aren't accurate, you can use average K-readings (~45) or keratometry from the fellow eye as a reasonable alternative.

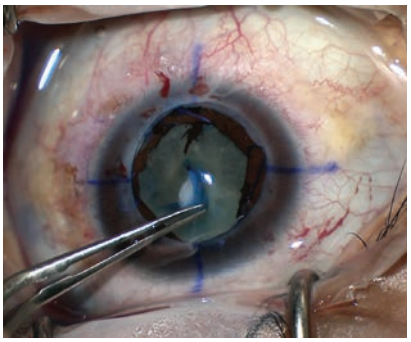


Figure 2. Trypan blue and a Malyugin ring can help with capsulorhexis formation during "open sky" surgery in patients with white cataracts and dense corneal opacity.

You should strongly consider using a three-piece IOL; such lenses provide several options in the event of anterior or posterior capsular compromises, including placement of the IOL in the sulcus, with or without optic capture and scleral fixation.

Surgically Speaking

In the operating room, two tactics have been shown to improve visualization: capsular staining and lighting adjustments. One study reported that the use of 0.06% trypan blue greatly improves BCVA in patients with corneal opacities.[5] Although instillation of this stain can make the capsule brittle, the payoff of improved visualization greatly outweighs the insignificant risks of this side effect.

Lighting adjustments that can improve visualization include the use of low to medium settings to reduce backscatter. In cases of significant corneal opacification, transcorneal oblique illumination is ideal.[6] The use of this newer strategy can greatly improve the view of the anterior chamber. Since it was first described,[7] this method has been shown to increase success in a wide range of anterior segment surgeries. The technique requires the use of a small-gauge light source, usually the light pipe used from a vitrectomy machine. The chandelier illumination is placed in the paracentesis; when used during capsular staining, it allows you to comfortably create a capsulorhexis and perform phacoemulsification.

To decrease the risk of anterior capsular tear or radialization during rhexis construction in your patient's eye, consider steps that can reduce posterior pressure:

- proper patient positioning;
- globe softening techniques;
- hyperosmotic agents; and
- an anterior vitrectomy.[8]

Additionally, start the rhexis with optimal visualization far from the opacity to ensure ideal initiation and control before proceeding toward areas with a poorer view.

Endothelial Challenges

In cases of endothelial dysfunction, most commonly seen in Fuchs' dystrophy concomitant with a visually significant cataract, we recommend performing combined procedures involving phacoemulsification and Descemet's stripping endothelial keratoplasty (DSEK)[9] or Descemet's membrane endothelial keratoplasty (DMEK).[10]

Combined approaches are more cost-effective, hasten visual recovery and prevent the need for multiple surgeries. One large study found no difference in complication rates, endothelial cell loss, graft success or visual improvement associated with either of these approaches, compared to sequential surgery (DMEK followed by cataract surgery).[11] Sequential surgery can also be considered in patients with significant astigmatism,

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as long as the cornea is stable before the IOL measurements and toric IOL implantation.

However, if you've got a patient who definitely needs a corneal transplant, but you're considering whether or not he'd benefit from a cataract procedure at the same time, keep in mind that endothelial transplant procedures alone can increase the risk of cataract formation, especially in patients over 50 who have shallow anterior chambers.[12]

Therefore, a transplant procedure alone should be considered more strongly in patients who have a lower risk of cataract formation (younger patients and patients with deep ACs). In older patients or those with shallow ACs, doing a combined procedure could be a better choice because earlier cataract formation is more of a risk in those individuals.

Combination Surgery Tips

If you combine DSEK/DMEK and cataract surgery in these patients, use cohesive viscoelastics to minimize interference with the graft, keeping in mind that dispersives are more difficult to remove completely. Avoid IOL optic damage to the graft by constructing a slightly smaller capsulorhexis and using intracameral miotics, minimizing anterior displacement of the IOL. Finally, note that hyperopic shifts have been noted after DSEK and DMEK.[13] A more myopic refractive target (-0.5 D to -1D for DMEK and -0.75 D to -1.5 D for DSEK) can facilitate emmetropia, if desired.

For patients with severe corneal scarring and opacification, combining penetrating keratoplasty with cataract extraction offers the expected benefits of preventing the need for a second surgery and decreasing the risk of endothelial cell loss.

However, understand that postoperative refractive outcomes are unpredictable and can be significantly disappointing after using this approach. One study demonstrated only a 62-percent rate of emmetropia within 2 D.[14]

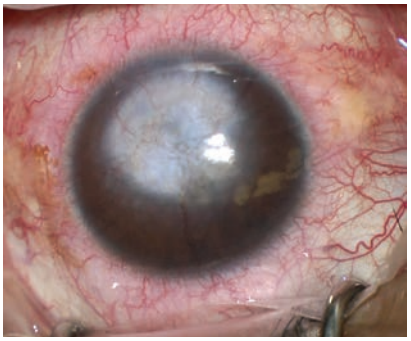

Figure 3. Corneal opacity that is too dense to perform phacoemulsification requires a PKP/phaco combination procedure.

Combination PKP and phacoemulsification can be considered in patients who are willing to wear contact lenses, desire rapid visual recovery and want to avoid multiple surgeries. Otherwise, sequential surgery after achievement of refractive stability (usually requiring at least one year) is preferred.

If stromal opacification is more anterior, keep in mind that deep anterior lamellar keratoplasty has been shown to produce more predictable refractive outcomes and faster visual recovery if combined with cataract surgery, compared to a combined PKP.[15] For patients with severe central corneal scarring—specifically in SJS and graft vs. host—consider extracapsular cataract extraction. If you pursue phacoemulsification, low aspiration settings are advisable. Suturing the wounds in these patients is also important.

No Magic Bullet

As you can see, cataract surgery through a "cloudy" cornea presents many challenges that require careful preoperative planning and intraoperative strategies to achieve a satisfactory visual outcome.

Although no single approach can guarantee success, by using the tips in this article, especially in appropriate combinations, you can minimize many avoidable, disappointing outcomes. REVIEW

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Dr. Naguib is a 2nd-year ophthalmology resident at the Baylor College of Medicine.

Neither Dr. Al-Mohtaseb nor Dr. Naguid report any relevant financial interest in any products mentioned.

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Recognizing Systemic Drug Side Effects

Christopher Kent, Senior Editor

Knowing what drugs your patient is taking is an important part of accurate diagnosis and successful treatment.

As every ophthalmologist knows, diagnosing ocular disease can be a challenge. One reason it's not always easy to nail the diagnosis is that patients are often being treated for other health concerns with drugs that can have ocular side effects.

"A variety of systemic medications cause ocular side effects," says Eric D. Donnenfeld, MD, an anterior segment specialist and clinical professor of ophthalmology at New York University Medical Center and a partner at Ophthalmic Consultants of Long Island. "Those side effects are real, and they're commonly underdiagnosed."

"Ocular side effects are much more common than you might expect," notes William F. Mieler, MD, Cless Family Professor of Ophthalmology and vice-chairman of the Department of Ophthalmology and Visual Sciences at the University of Illinois at Chicago. "Even ophthalmologists with a general practice will probably encounter an ocular side effect of a systemic medication once a week or so; which ones you encounter will depend partly on your practice. For example, in addition to seeing retina patients, I work in oncology, so I see numerous complications caused by cancer treatment medications. As you might imagine, those can be quite damaging."

Here, doctors with expertise in the ocular side effects of systemic medications share their experience with some of the drugs most often associated with ocular problems, and offer advice on how to proceed when you encounter them.

The Front of the Eye

Many systemic drugs are associated with dry-eye-related signs and symptoms, conjunctivitis and corneal problems.

• ***Oral diuretics.*** "A recent development that's been associated with ocular surface problems is a change in the primary therapy used to address high blood pressure," says Dr. Donnenfeld. "In the past, medications such as ACE inhibitors and calcium channel blockers were used as primary therapy for these patients. Now, the primary therapy is the use of oral diuretics. Oral diuretics have significant dry-eye side effects and also have been reported to contribute to open-angle glaucoma."

• ***Biologics.*** "A new medication called dupilumab [Dupixent, Regeneron], prescribed by dermatologists to treat atopic dermatitis, has been reported to cause conjunctivitis in about 20 percent of treated patients," says Stephen C. Pflugfelder, MD, a

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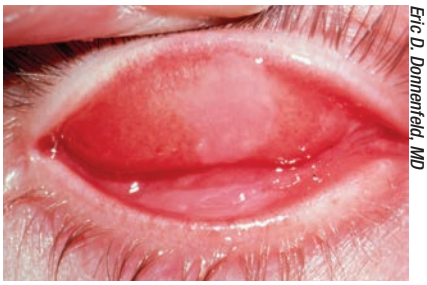


Eric D. Donnenfeld, MD

Membranous conjunctivitis in a patient with erythema multiforme minor due to the use of oral digoxin.

professor and director of the Ocular Surface Center at Baylor College of Medicine's Cullen Eye Institute in Houston. "Ironically, atopic dermatitis, an inflammatory skin condition, is itself associated with ocular comorbidities such as blepharitis, glaucoma, cataracts, retinal detachment and keratoconus, among other issues.

"Dupilumab is the first biologic treatment for atopic dermatitis," he explains. "In one study, dupilumab treatment was associated with a 5- to 28-percent increase in the incidence of conjunctivitis, compared to patients treated with placebo.[1] One case series found that 70 percent of patients treated with dupilumab developed anterior conjunctivitis.[2] Symptoms noted included burning, tearing and a decrease in visual acuity; signs included hyperemia of the limbus and conjunctiva.

"Options for managing these signs and symptoms include stopping the use of dupilumab, if the complications are severe," he adds. "If the dermatologist doesn't consider that a good option, some success has been reported treating with a topical steroid such as fluorometholone; tacrolimus ointment; or lifitegrast, if the patient doesn't tolerate the topical steroids."[1,3]

• ***Anticholinergics.*** Dr. Donnenfeld notes that these drugs may cause dry-eye symptoms. "The use of anticholinergics is very common," he points out. "Among other things, they're used to treat Parkinson's disease and used as stomach relaxants and anti-anxiety medications. They often cause significant dry-eye-related side effects that can't be addressed effectively with topical medications. Many times we have to go back to the internists and surgeons prescribing these medications and ask them to alter the treatment."

• ***Antihistamines.*** Dr. Donnenfeld notes that antihistamines such as Benadryl, commonly used to treat allergies, can trigger dry-eye symptoms.

• ***Amnioderone***. "Amnioderone is used to treat cardiac arrhythmias," Dr. Donnenfeld explains. "It can cause a whorl dystrophy of the corneal epithelium called vortex keratopathy that can decrease visual acuity. If the patient can't be taken off this therapy, the epithelium can be debrided to remove the offending whorl dystrophy." Dr. Donnenfeld also points out that amnioderone has been associated with ischemic optic neuropathy in some patients.

• ***Chemotherapy drugs.*** "Chemotherapy used to treat cancer will often damage the lacrimal glands, causing dry eye that can last for months," says Dr. Donnenfeld. "Furthermore, many patients receiving therapy for breast cancer are on anti-estrogen medications, and the resulting change in hormonal status can lead to dry eye as well." (Note: Chemotherapy drugs are powerful, and can cause a range of other ocular complications as well. For more on that, see the bullet point on page 45.)

Retinal Side Effects

Several dozen drugs have been associated with retinal toxicity or abnormalities. Among the drugs often associated with retinal damage are hydroxycholoroquine, thioridazine, bisphosphonates and phosphodiesterase-5 inhibitors.

• ***Hydroxychloroquine (Plaquenil).*** Retina specialists often encoun-

ter patients that have been treated with this medication, frequently prescribed by rheumatologists. "Most lupus patients are treated with hydroxychloroquine, and it's the main medication rheumatologists use that's been linked to side effects in the eye," says Vasileios C. Kyttaris, MD, assistant professor of medicine in the division of rheumatology at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. "It's very good for a milder type of lupus, and it's been shown to improve overall survival rates in lupus patients. Also, it's one of the few drugs for lupus—if not the only drug—that can be used during pregnancy. In the past we used the anti-malarial drug chloroquine for this purpose, especially for lupus with severe skin disease. But the incidence of maculopathy with that particular medication was quite high, so today we rarely use it.

"Unfortunately, over the years we've found that hydroxychloroquine isn't as safe as we used to think," he says. "Many lupus patients take hydroxychloroquine for several years, if not for life, and it seems to have a cumulative effect on the retina, causing maculopathy."

Dr. Kyttaris explains that this realization has caused rheumatologists to change what's considered a safe dose of the medication. "Prior to 2010, we used to recommend a dose of 6.5 mg per kg of body weight per day as the upper limit for hydroxychloroquine," he says. "However, it became apparent that this dose was too high for many people. The previous formula made sense for people with an ideal body weight, but a lot of overweight patients ended up being overdosed. So, the recommended dose has been decreased to 5 mg/kg/day. This change affects a lot of people, because about 70 percent of our lupus patients are on this medication.

"So far, it seems that this lower dose is safer," he notes. "For the first five years, the incidence of hydroxychloroquine retinopathy is now close to zero. Beyond that the risk of retinopathy increases, but it remains rare."

Dr. Kyttaris says that these patients should be examined by an ophthalmologist every year. "We want to make sure there's no early change in the macula suggestive of hydroxychloroquine toxicity," he explains. "We've found that if you wait for symptoms to appear—for the patient to complain of decreased vision, changes in color perception and so forth—the damage will be done. So the current standard is to have these patients screened once a year. The ophthalmologist checks the fundus, does color vision testing and does OCTs as well, although my understanding is that OCT may produce some false positive results. In fact, we're not sure if this type of maculopathy translates into clinically observable changes."

Dr. Mieler says that he sees numerous patients who are taking hydroxy-

Side Effects of Non-prescribed Drugs

William F. Mieler, MD, Cless Family Professor of Ophthalmology at the University of Illinois at Chicago, says that if you take a thorough patient history and find out which medications your patient is taking, there should be very few surprises. "However, there are times when patients are taking illicit drugs, or they're reluctant to admit they're taking something they find embarrassing," he says. "For example, some patients may not mention that they're taking erectile dysfunction drugs like Viagra or Cialis. Or they may not realize that something legal, but not advisable, is causing the problem, so they don't mention it.

"For example," he continues, "excessive caffeine intake can—rarely—lead to ocular damage. Some of the energy drinks that people take contain an enormous amount of caffeine. If someone's consuming a bunch of those energy drinks, the excessive amount of caffeine can cause a type of vascular occlusion, a rare condition called acute macular neuroretinopathy, indicated by little ischemic areas in the inner retina. Most of these patients will be missing part of their central or paracentral vision; they may report central visual blurriness. The signs and symptoms are subtle, but they're real. We've seen this in a number of patients who were ingesting an excessive quantity of those energy drinks.

"On some occasions you may also have to delve into the use of illicit medications," he notes. "Some illegal drugs can cause very significant vision problems, but a patient may not admit he's been ingesting something illegal unless there's a serious vision problem. Cocaine, for example, can cause arterial occlusions. This isn't common, but if you do cocaine long enough, it can happen. We've seen a number of cases where someone has been shooting cocaine for years. In that situation you can get deposition of particulate matter in the bloodstream; you can see the actual particles on the retina. Crack cocaine can also produce an ischemic process in the inner retina.

"When you see changes like this," he says, "you need to ask the patient: 'In addition to medications you're taking, do you do illicit drugs?' Of course, the patient may deny it. You have to make sure that patients in this situation understand that this is hurting their vision and might lead to blindness. We've confronted a number of people, saying, 'It's really in your best interest to tell us what you've been doing, because otherwise we can't help you.' Once they understand the seriousness of the situation, most patients will admit what they've been doing. You have to let them know that you're not trying to implicate them; rather, you're just trying to find out what's causing the problem and help them. They're especially likely to cooperate if they've come to you with a visual problem that they want to get to the bottom of."

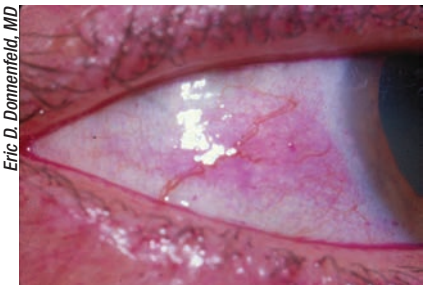
—CK

chloroquine for arthritic conditions or systemic lupus erythematous. "How we proceed with these patients depends upon how long the patient has been taking hydroxychloroquine, the dosage of the medication, and whether we find any features of toxicity," he explains. "Michael Marmor, MD, and I, among others, published detailed guidelines for managing this problem back in 2016, on behalf of the American Academy of Ophthalmology.[4]

"Once you realize that a patient is taking hydroxychloroquine, you monitor for signs of toxicity," he says. "If there are no features, you keep monitoring. If you do find signs of toxicity, you talk to the prescribing physician and try to stop the medication. That's key, because once problems arise, you can't undo the damage. There's no treatment for the toxicity once it has occurred, and sometimes it gets worse if the patient is left on the medication."

Dr. Kyttaris notes that there are other treatment options if a patient taking hydroxychloroquine is developing maculopathy. "We may switch the patient to quinacrine, which is an anti-malarial that hasn't been shown to cause problems with the macula," he says. "Quinacrine is an older drug, and it's a compounded formulation, which means we have to get it from a compounding pharmacy. We have issues with insurance covering it, but it can work in this situation. If we can't use that, we have to use immunosuppressant drugs like azathioprine or low-dose methotrexate to control the disease."

• ***Phosphodiesterase-5 inhibitors.*** "These include erectile dysfunction drugs like sildenafil (Viagra) and tadalafil (Cialis)," notes Dr. Donnenfeld. "They've been associated with ischemic optic neuropathy, and they can cause changes in photoreceptors, resulting in a change in vision that many patients describe as 'blue vision.' "



Eric D. Donnenfeld, MD

Rose bengal staining of the conjunctiva in a patient with dry-eye disease secondary to oral diuretics.

• ***Thioridazine***. "Another big category is medications used to treat psychiatric disorders," notes Dr. Mieler. "Thioridazine (Mellaril) can produce a profound toxicity. We see a couple of cases of that every year. That drug can cause significant loss of retinal pigment epithelium and loss of vision."

• ***Bisphosphonates***. "There have been some unconfirmed reports that bisphosphonates, which we use to treat osteoporosis, have been linked with uveitis," says Dr. Kyttaris. "Because those reports haven't been confirmed, we still use these drugs on patients, even those with a history of uveitis. However, we're aware of the issue."

• ***Tetracycline***. Drugs in this class include doxycycline, which may be prescribed by ophthalmologists. "I often prescribe doxycycline or tetracycline for patients who have ocular surface disease," says Dr. Donnenfeld. "These drugs are very effective—but they can also cause papilledema and enlarged ventricles. So some of the medications we use in ophthalmology have significant side effects as well."

Other Ocular Side Effects

Additional drug side effects include cataract, glaucoma, floppy iris syndrome, keratitis, uveitis and alterations of blood flow.

• ***Tamsulosin***. Tamsulosin is a side-effect-prone oral medication that most ophthalmologists are familiar with. "Tamsulosin is used to treat prostate enlargement and urinary flow in men," says Dr. Donnenfeld. "Every ophthalmologist knows that this drug is strongly associated with intraoperative floppy iris syndrome, or IFIS. Other medications in the same drug class—alpha-blockers—such as silodosin, alfuzonsin and terazosin, can also cause this problem. The herbal supplement saw palmetto has been associated with this as well. Its use is more common than you might suppose.

"An interesting note about the IFIS side effect is that it doesn't seem to be dose-dependent," he continues. "A single dose of drug can cause it. In the past, some ophthalmologists have recommended that the medication be stopped prior to surgery, but in my experience, stopping the medication has very little effect. The IFIS doesn't improve. As a result, once a patient has taken the drug we're forced to deal with the floppy iris during surgery. We use very aggressive dilation, nonsteroidals and Omidria [Omeros] to improve iris tone and reduce the need for iris hooks and rings."

• ***Oral corticosteroids.*** "As we all know, corticosteroids can raise IOP, but more commonly they lead to cataracts," says Dr. Donnenfeld. "The most common cataract associated with oral corticosteroids is the posterior subcapsular cataract. Stopping the steroid won't undo whatever damage has been done, but it should stop the progression."

Dr. Kyttaris notes that corticosteroids, including prednisone and prednisolone, are also used by rheumatologists. "Over the years we've limited our use of these drugs because of their side effects," he says. "In the eye, these drugs are associated with problems in the anterior segment—unlike hydroxychloroquine, which tends to affect the retina. Steroids can increase both the incidence and progression of cataracts, and they can induce glaucoma by increasing intraocular pressure.

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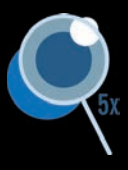

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Side Effects of Some Common Medications

Medication	Used to treat	Side effects	Visual signs and symptoms
Amnioderone	Ventricular tachycardia and atrial fibrillation	Corneal verticillata, lenticular opacities; possibly optic neuropathy	Corneal deposits, whorl keratopathy
Bisphosphonates	Osteoporosis, Paget's disease, metastatic bone disease, multiple myeloma	Scleritis, conjunctivitis, anterior uveitis	Blurred vision, ocular pain
Digoxin	Atrial fibrillation, congestive heart failure	Decreased visual acuity, central scotoma, color vision defects	Yellow vision, flashing lights, hazy vision, difficulty reading
Direct-acting oral anticoagulants	Venous thromboembolism, atrial fibrillation	Ocular toxicity	Blurred vision, keratoconjunctivitis, subconjunctival and retinal hemorrhage
Ethambutol	Tuberculosis	Optic neuropathy	Bilateral central vision loss, scotomas
Fingolimod	Mutiple sclerosis	Possible cystoid macular edema	Blurry vision, central blind spot, sensitivity
Hydroxychloroquine	Rheumatoid arthritis, lupus erythematosus and Sjögren's syndrome	Retinal toxicity, bilateral bull's-eye maculopathy	Difficulty focusing, streaks or flashes, swelling, eye color changes
Isotretinoin	Acne and psoriasis	Meibomian gland dysfunction, intracranial hypertension	Blurred vision, headaches, tinnitus
Phosphodiesterase Inhibitors	Erectile dysfunction	Possible ischemic optic neuropathy (infrequent at low doses)	Bluish tinge to vision, light sensitivity
Tamoxifen	Metastatic breast cancer	Retinopathy, possibly cataract, intraretinal crystalline deposits	Corneal dryness, floaters, decreased visual acuity and color vision
Tamsulosin	Benign prostate hyperplasia	Floppy iris syndrome	Blurred vision
Topiramate	Migraines, seizures, bipolar disease, post-traumatic stress, obsessive-compulsive disorders	Ciliary body effusion and anterior rotation of the ciliary processes, angle-closure glaucoma, maculopathy	Blurred vision, diplopia, vision disturbances, myopic shift
Vigabatrin	Seizures not responding to other therapies	Progressive bilateral concentric visual-field constriction	Reduction of visual acuity
Warfarin	Risk of recurrent heart attack or stroke	Ocular toxicity	Subconjunctival and retinal hemorrhage

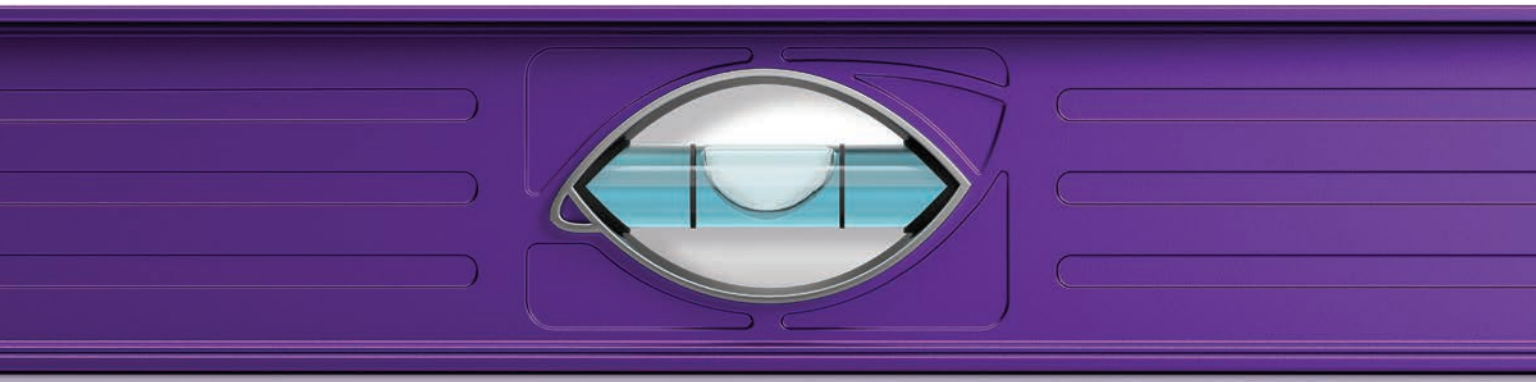
Of course, steroids can also affect the eye indirectly by inducing or worsening diabetes, which can then cause diabetic retinopathy.

"Unlike the use of hydroxychloroquine, our professional societies haven't offered any clear-cut recommendations regarding ophthalmologic screenings for patients using steroids," he adds. "I think a lot of rheumatology patients on steroids don't necessarily get close pharmacological follow-ups unless they develop problems. That's something we may need to change in the future."

Dr. Kyttaris suggests that ophthalmologists keep in mind that most patients being treated for rheumatoid disease are taking steroids, at least intermittently. "It's certainly possible that some of what you see is a steroid side effect," he notes. "If you identify this connection, you can make the rheumatologist aware of it. Then we can try to get the patient to as low a steroid dose as possible, or in some cases take the patient off steroids altogether."

• ***Immunosuppressive medications.*** Dr. Kyttaris notes that immunosuppressive medications like methotrexate, azathioprine and leflunomide are routinely used to treat rheumatoid arthritis, and this type of drug has been associated with infectious complications in the eyes. "This can be a problem, especially if the patient has Sjögren's syndrome, which is very common in rheumatic diseases," he says. "The combination of dry eyes, primary or secondary Sjögren's syndrome and the use of an immunosuppressive drug has been linked to infections such as blepharitis in the eye."

Dr. Kyttaris points out that the situation is confused somewhat by the reality that many rheumatologic diseases can produce ocular effects such as inflammation on their own—perhaps giving the impression that the drug used to treat the disease has caused the problem. "Many ocular problems such as uveitis, and sometimes scleritis and conjunctivitis, are associated with inflammatory rheumatoid diseases such as rheumatoid arthritis and spondyloarthropathy," he says. "However, we don't see these effects as often as we used to because we have better treatments for the diseases. If the systemic disease is well-controlled, ocular inflammatory symptoms are also controlled."



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[a]**STUDY DESIGN:** The efficacy and safety of FLAREX (n=41) vs FML* (n=37) were evaluated in a randomized, double-blind clinical trial in 78 patients with ocular surface inflammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes. In a separate randomized, double-blind clinical trial in 82 patients with ocular surface inflammation in one or both eyes, the efficacy and safety of FLAREX (n=37) vs prednisolone acetate 1.0% (n=45) were evaluated. In these studies, patients administered either FLAREX or FML*/prednisolone acetate 1.0% 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. At each visit, investigators determined if symptoms in the involved eye were resolved (cured), improved, unchanged, or worsened. If a patient was rated as cured before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.[2]

[b]Cost information based on Wholesale Acquisition Cost (WAC), 2019 data.

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

WARNINGS AND PRECAUTIONS
Topical Ophthalmic Use Only
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Prolonged use may result in glaucoma, damage to the optic nerve, and defects in visual acuity and visual field. It is advisable that the intraocular pressure be checked frequently.

Cataracts
Use of corticosteroids may result in cataract formation.

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

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

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

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

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

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References: 1. FLAREX [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017. **2.** Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol*. 1984;16(12):1110-1115. **3.** Data on file. Fort Worth, TX: Eyevance Pharmaceuticals LLC. **4.** US Department of Health and Human Services, Food and Drug Administration. *Approved drug products with therapeutic equivalence evaluations*. (Orange Book). 38th ed. Washington, DC: US Department of Health and Human Services, Food and Drug Administration; 2018.

FLA-09-19-AD-39

New Drugs and Their Side Effects: Staying Informed

Eric D. Donnenfeld, MD, clinical professor of ophthalmology at New York University Medical Center, notes that ophthalmologists are usually aware of the most common drug side-effect associations. "However, when a new medication becomes available we may not know the ocular side effects until after we've had time to learn a little more about it," he says.

"Surprising new findings and associations are discovered and recognized all the time," agrees William F. Mieler, MD, Cless Family Professor of Ophthalmology at the University of Illinois at Chicago. "For example, there's a medication called pentosan polysulfate that's used to treat cystitis in females. It's been around since about 1997. In recent years, doctors observed macular pigment mottling in some of these patients; it was initially believed to be a form of macular degeneration. Only recently did we realize that this is a side effect of the pentosan. It was difficult to see the connection, as it takes about 12 to 15 years before the side effect occurs. That's why it's only coming to light now. Fortunately, this particular problem is rare."

Dr. Donnenfeld points out that organizations like the American Society of Cataract and Refractive Surgery and the American Academy of Ophthalmology are a great resource for staying educated about the latest systemic drug side effects. "That's another reason it's important to attend the main conferences," he says. "Staying on top of the literature also is important, and online forums may provide useful information. Beyond that, you can refer to the Physicians' Desk Reference for more detailed information about specific side effects."

—CK

• ***Chemotherapy agents.*** In addition to the dry eye mentioned earlier, these drugs can induce a range of ocular complications, including blurred vision; cataract; conjunctivitis; corneal ulcer; extraocular muscle paresis; eye pain; glaucoma; optic nerve disorder; retinal detachment; retinal tear; retinal vascular disorders; uveitis; and vitreous hemorrhage.[5]

Strategies for Success

These strategies will help ensure that drug side effects are correctly identified and addressed:

• ***Review the patient's medication usage history carefully.*** "Taking a systemic drug history is an important part of understanding a patient's ocular findings," says Dr. Donnenfeld. "I suspect that medication side effects are most likely to be found in cases of dry eye, and sometimes in glaucoma. I think it all comes down to the nature of the patient's ocular problem and knowing what other therapies the patient is on—and whether they can be altered."

• ***If you're not sure about a drug association, try stopping the systemic medication—if possible.*** "If you encounter a sign or symptom and you're really not sure whether the medication is to blame, stop the medication if you can, and see if the problem goes away," Dr. Donnenfeld suggests.

• ***Take special note if the patient is being immunosuppressed.*** "If an immunosuppressed patient has an active eye infection that's not responding to measures such as a topical or systemic antibiotic, the ophthalmologist should discuss this with the patient's rheumatologist," says Dr. Kyttaris. "It may be possible for the patient to at least get off the immunosuppressor temporarily, so the infection is better dealt with."

• ***Be careful when diagnosing hydroxychloroquine toxicity.*** "It's important to be sure that the maculopathy is really being caused by the hydroxychloroquine treatment," says Dr. Kyttaris. "Hydroxychloroquine really helps many of our patients, so we don't want to stop it if we don't have to."

• ***If a patient isn't responding to therapy, consider the possibility that a medication may be responsible for the problem.*** Dr. Donnenfeld notes that it's easy to overlook the possibility that a problem is actually being caused by a systemic medication. "If you find that a patient isn't responding to therapy the way you think she should, take another look at her systemic medications," he says. "You may spot a reason for her problem."

Keeping Your Eyes Open

"The key is to always get a thorough history listing what the patient is taking—legal or illegal," Dr. Mieler concludes. "As long as you have a good base of knowledge and an index of suspicion, it's rare that you'll miss something. You just have to ask the right questions and understand the associations between the medications and the problems you might see." REVIEW

Drs. Kyttaris, Mieler and Pflugfelder report no financial ties to any product mentioned. Dr. Donnenfeld is a consultant for Omeros.

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Review Turns 25: A Look Back

Review Staff

Review's editors reflect on topics that influenced ophthalmology over the first 25 years of the magazine.

The year was 1994 … Nelson Mandella was elected President of South Africa, the Northridge Earthquake rocked California, Tonya Harding was stripped of her skating championship for having her rival, Nancy Kerrigan, attacked; the Channel Tunnel finally opened, connecting England to France; the iconic television show "Friends" debuted; and people flocked to theaters to see "The Lion King," "Forrest Gump," and the "The Shawshank Redemption." Also, in April of 1994, *Review of Ophthalmology* premiered, under the hand of late Publisher Rick Bay, Editor-in-Chief Stan Herrin and Chief Medical Editor Mark Blecher, MD. (*Review*'s current EIC, Walter Bethke, joined the staff a month later as a junior editor.)

Here's a look back at some of the developments we've covered over the past 25 years and how they've shaped ophthalmology.

Health-care Reform

One of the first ways the mainstream news of 1994 intersected with ophthalmology was First Lady Hillary Clinton's push for health-care reform, eventually dubbed "Hillarycare" by pundits.

Among other provisions, the Health Security Act, as it was called, would require all citizens to have health care, and all employers to provide it (with financial assistance for small businesses). Cooperatives in each state would sell insurance plans to citizens and oversee insurance companies, and a National Health Board would control spending and oversee the entire operation.[1,2]

Organized ophthalmology took issue with one provision of the plan that proposed establishment of cataract "Centers of Excellence"—surgical centers in urban areas that would be able to perform cataract surgery, coronary artery bypasses and other procedures for less cost to Medicare. The American Society of Cataract and Refractive surgery opposed this provision. A news article from *Review*'s second issue stated ASCRS's opposition to the Centers on the following grounds: " 'Centers of Excellence' implies that

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providers sanctioned by the government would offer a higher quality of care than other physicians in the same area; Medicare would also pay beneficiaries to seek care at these centers; the provision is an unnecessary and unfair government intrusion into the marketplace, because smaller providers will not be able to compete with the Centers; by focusing only on the competition the Centers will foster, supporters are focusing only on cost and not on the issues of quality and access." Ultimately, much to the chagrin of Mrs. Clinton and her task force, but maybe to the relief of ASCRS members, the bill was nixed in the fall of 1994.

In 1993, *Review* editorial board member Jeffrey Morris, MD, MPH, was on the Clintons' health-care task force. The Clintons' health-care bill failed to gain popularity and ultimately didn't come to pass. "After you shave away all the mind-numbing details," wrote Dr. Morris in a September 1996 feature on Mr. Clinton's bid for a second term, "the underlying concept of President Clinton's proposal was simple: Shift power away from big employers and insurance companies and give it to patients and physician networks."

A lot of ink was also devoted to the specter of managed care, which, to hear some observers tell it, appeared to be growing like a deadly virus in a host body. Articles with titles such as, "Will Your Patients Go to a Medicare HMO?", "Yes You Can Profit from Managed Care Plans," "How I Succeed in a Managed Care World," and "Why I Joined Forces with the Enemy," filled each issue.

In our premiere issue, cataract and refractive pioneer Richard Lindstrom, MD, dispensed tips on existing in the brave new world of managed care. Among them were "lower your standard of living," diversify your income stream by offering refractive surgery, invest in real estate and businesses other than your own; and lobby your state legislature. "Adapting to managed care isn't easy. It's hard," Dr. Lindstrom wrote. "However, practicing under managed care can still be rewarding, as long as you are proactive. Fortune will favor you if you're prepared, and 80 percent of success is being in the right place at the right time. Make sure you do both and you'll do fine under managed care." Soothsayers who saw the writing on the wall and positioned themselves to succeed in managed care were ultimately proven right: Today, more than 80 percent of covered individuals are in a managed-care plan, according to the latest data from Managed Care Online.[3]

Refractive/Cataract Rewind

In the mid-90s, phaco was providing the buzz in cataract surgery, with the magazine featuring many discussions on innovative ways to break up the nucleus.

Two surgeons offered creative takes on cataract surgery in our June 1994 issue. First, Danville, Illinois, surgeon Dave Dillman likened his approach to cataract surgery to a golfer who "uses all 14 clubs." "I'll wager you'll never see a professional golfer in a tournament play the course with

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only four clubs in his or her bag…" he wrote. "I like to think of cataract surgeons as 'professionals' as well, and yet, I wonder how many of our 'pros' walk into the operating room with only four clubs in their bag? My guess is way too many. So, let's discuss how we can identify and use the variables, the 'clubs, [the balance of fluid ingress and egress, aspiration flow rate and followability, the right phaco needle for the right situation and others] that are available to us during phacoemulsification."

In the same issue, Boca Raton, Florida, surgeon Alan Aker advocated a unique approach that drew on Eastern philosophies to allow cataract surgeons an almost Zen-like mastery over their procedures. Though the article is old, the advice remains fresh. Drawing on the work of psychologist Albert Bandura, Dr. Aker wrote that the people most successful in life don't just have raw talent, but possess several other qualities: persistence, even in the face of difficulties and setbacks (such as a torn capsule); an understanding of, and belief in, their own capabilities in order to motivate them; and they all have a philosophy of constant self-improvement. "They methodically analyzed their setbacks and learned from their mistakes," Dr. Aker wrote.

In addition to beginning to embrace topical anesthesia and clear corneal incisions for more of their cases, following are some other steps in cataract surgery's evolution that *Review* covered over the years:

• ***Phaco technology.*** Though phaco had been around since the late 1960s thanks to Charles Kelman, MD, the 1990s and early 2000s saw a flurry of innovations both in techniques and technology that kept surgeons constantly exchanging new thoughts on the subject. There seemed to be a new phaco machine almost every year.

One of the main problems both manufacturers and surgeons alike constantly contended with was occlusion breaks and post-occlusion surges. In response came inventions such as dual-linear-control footpedals and phaco burst on Bausch + Lomb's machines, NeoSonix on the Alcon Legacy, "sonic phaco" on the Staar Wave device and WhiteStar phaco on the (then) AMO Sovereign. These incremental changes led to the features on the Alcon Centurion, the B + L Stellaris Elite and the WhiteStar Signature Pro from Johnson and Johnson Vision that surgeons use today.

Around this time, micro-incision, or "bimanual," phaco also grabbed some surgeons' interest. But, as Cincinnati's Robert Osher, MD, said in an article from that period, more pieces of the puzzle needed to be in place for micro-phaco to take off: "When we have a superior lens to fit through a 1.2- to 1.5-mm incision," Dr. Osher said, "then micro-phaco will become the standard of care."

• ***Tackling spherical aberration.*** Also in the early 2000s, lens researchers began to think there was more to postop cataract surgery vision than just acuity, and that spherical aberration may have a hand in the quality of patients' vision. This led to the eventual trial and approval of the AMO Tecnis IOL (now made by Johnson & Johnson Vision), which was designed to counteract the positive spherical aberration present in the cornea. Approvals of the B+L SofPort AO and the Alcon AcrySof IQ followed. Though they each took different approaches to handling a patient's SA, many surgeons saw value in the idea. "The need to manipulate spherical aberration derives from the improved clarity of vision (or contrast) under mesopic and photopic conditions," wrote Ontario's George H.H. Beiko, BM, BCh, FRCSC, in a *Review* article on the topic in 2008, "as well as the improved functional performance under night driving conditions."

Dave Dillman, MD's phaco golf bag.

• ***Premium IOLs.*** In the United States, cataract surgery in general, and premium intraocular lenses in particular, took a major step forward in November of 1998 when the first toric intraocular lens, the Staar Toric IOL, was approved. As Sarasota, Florida, surgeon and Staar investigator Harry Grabow commented in *Review*'s December 1998 issue, "Few surgeons actually do AK at the time of surgery," he said, noting that many surgeons would feel more comfortable with the idea of correcting astigmatism with a lens. "The correction for astigmatism is a fixed and known value in the implant, so we're not dependent on corneal healing, age or the depth of our incisions as variables," Dr. Grabow added. "The only variable is the final position of the IOL."

The Staar Toric proved to be the tip of the iceberg, with many toric lenses and presbyopic-correcting IOLs from the other major manufacturers following it in the years to come. The first multifocals approved were AMO's ReZoom and Alcon's ReSTOR, soon followed by the Tecnis MF and the Crystalens from B+L, leading up to today's most recently approved technologies: the Tecnis Symfony and the Alcon PanOptix trifocal.

An innovative technology that *Review* has followed closely since 2002 is the adjustable IOL from RxSight, formerly called the Calhoun Lens. The lens's power can be manipulated after implantation via a special light-delivery

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- The percentage of patients who received **DEXYCU®** (dexamethasone intraocular suspension) 9% (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (n=94/156) vs 20% (n=16/80) in the placebo group[1]
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) at day 30 was significantly lower in the **DEXYCU** (517 mcg) treatment group (20%; n=31/156) compared to placebo (54%; n=43/80)[1]

*DEXYCU was studied in a randomized, double-masked, placebo-controlled trial. Patients received either DEXYCU or a vehicle administered by a physician at the end of the surgical procedure. The primary endpoint was the proportion of patients with anterior chamber cell clearing (cell score=0) on postoperative day 8.

INDICATION AND USAGE

DEXYCU® (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure
- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection
- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression
- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

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

References: 1. DEXYCU® (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. December 2018. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology.* 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

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DEXYCU (dexamethasone intraocular suspension) 9%,
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Initial U.S. Approval: 1958

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

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing

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

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires 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 of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

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

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warning and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

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device until the patient's happy with the result. "It's FDA-approved and seeing a slow commercial release in the United States," notes *Review*'s cataract and refractive editor Arturo Chayet, MD, who took part in the lens's clinical studies.

• ***Femtosecond cataract.*** This technology made a big splash when it appeared, especially with its ability to create circular capsulorhexes. Some surgeons rushed to adapt their techniques to use it, while others adopted a wait-and-see attitude, stating that they'd like to see more definitive femtosecond-cataract results in the literature that would tip them over to the FLACS camp. In our March 2015 issue, a surgeon who took part in a Veterans Administration meta-analysis of peer-reviewed literature on FLACS to help determine whether the VA would implement it chimed in. "In terms of other complications, femtosecond and conventional surgery had the same adverse events and the rates of complications were comparable between the two," said Ken Gleitsmann, MD, an ophthalmologist from Hilton Head Island, South Carolina, one of the report's co-authors. "However, a lot of this has to do with the small size of the study groups. As femtosecond goes out into the marketplace and you have a million cases to look at, things may look a little different. Also, making things more difficult is the fact that the complication rates with conventional surgery are so low; to get something even lower than that is difficult."

Though surgeons say both manual cataract surgery/phaco and FLACS produce very good outcomes, the latter may be the go-to in challenging cases with pseudoexfoliation and brunescent lenses. Despite this, many surgeons remain on the fence.

• ***Excimer-based refractive surgery.*** In October of 1995, the Summit excimer laser fired the pulse heard 'round the world and became the first laser approved for photorefractive keratectomy in the United States. "The concept of using a high-tech laser to 'sculpt' corneal tissue has captured the imagination of doctors, financial investors, journalists and the public like no other procedure or device in ophthalmic history," wrote Jack Persico, then *Review*'s special projects editor in a feature about the potential of the new procedure. Three years later, LASIK would be approved, touching off debates over which procedure was better, such as the "Point-Counterpoint" in our April 1995 issue, written before LASIK was officially approved, when it was known as laser ALK or ALK-E *(excerpts from it appear to the left).*

Though LASIK would go on to become the dominant refractive surgery procedure in the country, the emergence of ectasia in some cases eventually let PRK up off the mat and back into the refractive surgeon's armamentarium as a trusty alternative for certain patients. Relatively recently, small-incision lenticular extraction, or SMILE, has arrived, vying for a seat at

Remember when ...

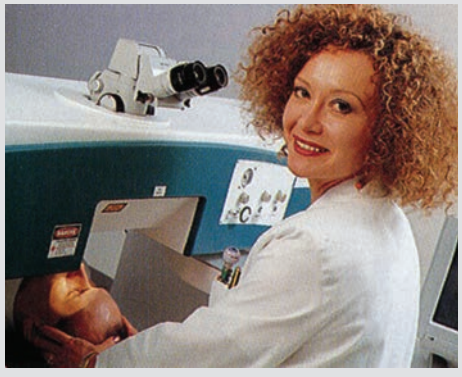
... the FTC investigated radial keratotomy advertising?

In October 1994, The FTC thought RK practitioners were getting a little carried away with the procedure—now a distant memory— and started evaluating claims that RK:

- Eliminates the need for corrective lenses;
- Offers permanent, proven and/or predictable vision correction;
- Is a highly precise microsurgical procedure;
- Is a procedure that has advanced; and
- Has been performed on more than 1 million people. *(Source: Sept. 1994 ASCRS/ASOA Washington Newsletter)*

A Heavyweight Bout, Circa 1995: ALK-E vs. PRK

"The excimer is an incredibly precise instrument, capable of removing tissue to within 0.25 µm of the intended amount," wrote Houston surgeon Stephen Slade in *Review*'s April 1995 issue. "Unfortunately, in surface PRK, that surgical precision frequently doesn't translate to a precise refractive result."



As a retort, Marguerite McDonald, MD, then still in New Orleans, wrote, "[ALK-E] is much more difficult to perform than a straight 'surface' PRK, and the manufacturers have yet to make a microkeratome that's foolproof."

the table, with some surgeons arguing it has advantages over LASIK.

A Revolution in Retina

Carl Regillo, MD, the director of Wills Eye Hospital's retina service, and co-editor of *Review*'s Retinal Insider department, recalls what it was like treating wet age-related macular degeneration patients in 1994. "We would examine most of them once and say, 'Sorry. We can't do anything for you,' " Dr. Regillo says. "It was a hard conversation to have, telling these patients they would be experiencing severe vision loss in another 12 to 18 months." The best he could do was refer them to a low-vision specialist, knowing that even the most sophisticated magnifying devices wouldn't stop 90 percent of them from going blind.

Since then, retinal care has undergone a sea change, resulting in greatly improved outcomes and continually increasing patient and clinician expectations. Advances in injectable anti-VEGF therapy, continuing to this day, have enabled Dr. Regillo and his colleagues to save and actually improve the vision of thousands of patients once doomed to live out their lives without vision. Miniaturization of surgical instruments, refined surgical techniques and improved diagnostic equipment have combined with the new therapy to put retinal practice at the forefront of modern eye care.

"Retina has undergone a virtual revolution in just about every aspect of our practices in the past 20 to 25 years," says Dr. Regillo. "It's nothing short of amazing."

"[PDT] was the first significant step forward in achieving better outcomes for wet AMD patients," he reflects. "All of a sudden, AMD became a routine manageable condition." As the early years of the 21st century unfolded, ongoing progress soon included the treatment of diabetic retinopathy and retinal vein occlusion with intraocular injections of steroids.

Meanwhile, in advance of the historic debut of anti-VEGF therapy, the first optical coherence tomographers made their way into retina specialists' offices, and eventually helped establish a new standard of care. "OCT was a landmark advance in diagnostics," Dr. Regillo says. "It arrived at the perfect time for us, when anti-VEGF therapy was coming into our hands."

After Macugen had its brief moment in the sun, Dr. Regillo says 2006 was another milestone year, introducing a second wave of anti-VEGF therapies. "We saw a major leap forward for wet AMD," he recalls. "Lucentis replaced Macugen that year, and soon Avastin (bevacizumab) and Lucentis (ranibizumab) powered our therapeutic practices like never before."

In 2011, Eylea (aflibercept) was released and approved to provide effective treatment for diabetic retinopathy, diabetic macular edema, wet AMD and macular edema following retinal vein occlusion. "Now we could confidently treat wet AMD, DME, and RVO—the three most common medical retinal conditions," he says. "Eylea, Avastin, and Lucentis emerged as the so-called pan-VEGF-A blockers."

Besides the landmark emergence of anti-VEGF therapy, Dr. Regillo says the ability to view surgery on a 3D screen rather than through the microscope, as well as small-incision, trocar-based surgery and widefield viewing have each made an impact.

"Of all the advances on the surgical side, obviously, the introduction of small incision, trocar-based vitrectomy surgery has been very significant," he says. "But couple that with modern widefield viewing, and I think you can say today's surgery is revolutionary. Widefield viewing is probably one of the biggest advances in allowing us to be much more capable, because, as surgeons always say, 'You can't treat what you can't see.' "

Reflections on Glaucoma

Peter Netland, MD, PhD, professor and chair, University of Virginia School of Medicine, and *Review*'s Glaucoma Management co-editor, reflects on the changes physicians have witnessed since the 1990s.

"In glaucoma, we monitored pa-

Land of the Lost

Over the years, some technology, like excimers and phaco, has stood the test of time. Some has not. Here are a few from the latter category:

- *Novatec laser.* This rapidly scanning, solid-state laser aspired to provide custom ablations, but never achieved approval in the era of excimer LASIK and PRK.
- *Picosecond laser.* Playfully dubbed the "Swiss army knife" of ophthalmology, the picosecond was approved for capsulotomies and iridotomies as early as 1994, but the brass ring of refractive correction always seemed to be out of reach.
- *Holmium laser thermokeratoplasty.* Designed as a treatment for hyperopia, it could never overcome issues with unpredictability and regression of effect.
- *Apple's Newton Messagepad and the Sharp Wizard.* Apple doesn't always hit home runs, as evidenced by the clunky Newton (right), introduced in 1994. It's notable, though, as a sign of things to come: The company had created a "palmtop" computer that let you to access your e-mail and serve as personal organizer. Newtown's competitor, the Sharp Wizard, offered similar functions, as well as the ability to sketch on its LCD screen.

—Staff

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Point: Limbal Anterior Vitrectomy vs. Pars Plana Vitrectomy

Rely on Limbal Anterior Vitrectomy

By Robert Maloney, MD, MA
Los Angeles

I'm concerned to see how often pars plana vitrectomy is promoted as the optimal approach to vitrectomy for the anterior segment surgeon. Pars plana vitrectomy carries some serious risks, such as retinal tears and detachments. These are unnecessary chances to take, since most cases that require vitrectomy can easily be handled by a limbal approach. In this article, I'll explain why the limbal approach is preferable for most patients.

No Problems with Vitreous

The most significant reason given for anterior segment surgeons to do pars plana vitrectomy is that limbal vitrectomy causes vitreous to come forward into the anterior chamber. This is not true. If there's a central tear in the posterior chamber—or no posterior capsule—the vitreous can be managed without difficulty by using a limbal approach. With bimanual instruments, make watertight paracenteses and place the port of the vitrectomy cutter well behind the posterior capsule. You'll clean up the vitreous without bringing any of it forward into the anterior chamber. The idea that vitreous will continue moving forward is a misconception arising from three sources:

• ***Source 1: Surgeons place the cutting port too anteriorly.*** Vitreous comes to the cutting port of your aspirating handpiece, meaning it moves to wherever you put the port. If you perform a limbal vitrectomy and put the port behind the posterior capsule, vitreous won't come forward. However, surgeons tend to place the vitrectomy port in the iris plane, where, of course, the port will pull the vitreous forward. It's fine to start in the iris plane, but the surgeon should move the port posteriorly, cutting all the while to avoid traction, until the port is well behind the posterior capsular opening. Ideally, the port is just anterior to the most posterior focal plane of the operating microscope. This location is in the anterior third of the vitreous, where it's not possible to cut the posterior capsule or iris. Vitreous will then stay in the posterior chamber.

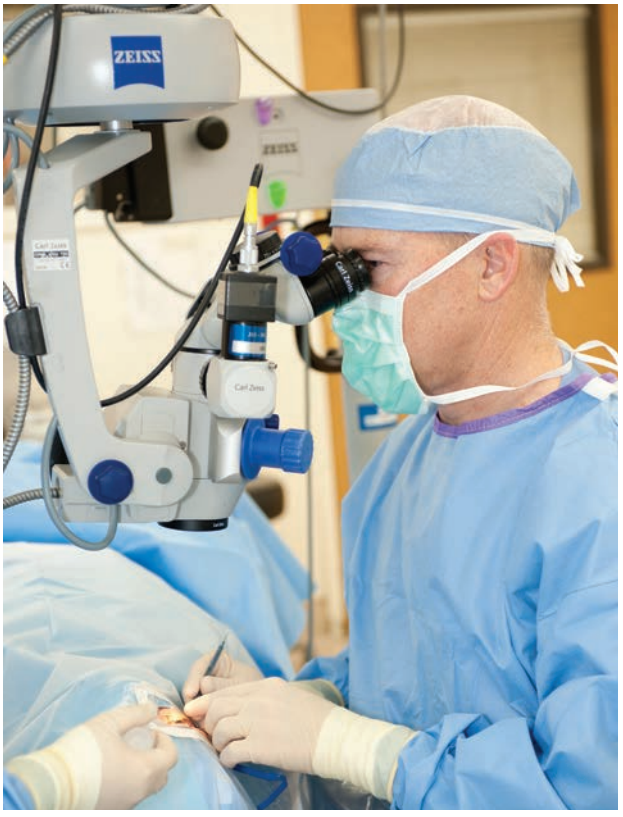

Figure 1. If Dr. Maloney needs to perform an anterior vitrectomy, only a few factors will prevent him from taking a limbal approach.

This article has no commercial sponsorship.

Counterpoint: Limbal Anterior Vitrectomy vs. Pars Plana Vitrectomy

Pars Plana is the Better Approach

Steve Charles, MD
Germantown, Tenn.

There is currently a controversy concerning whether the vitreous cutter should be used through a limbal sideport or the pars plana when anterior vitrectomy is required during cataract surgery. Though the former may seem more appealing to the typical anterior segment surgeon, it has several disadvantages that make a pars plana approach better. Here, I'll explain the benefits of pars plana in detail and provide insights on challenges you'll need to meet if and when you use this preferred method for anterior vitrectomy.

The Drawbacks of Limbal

Pars plana is the better approach because it involves less endothelial trauma caused by turbulence, more complete anterior vitrectomy because of posterior movement of the vitreous and less risk of iris and capsule damage from direct contact with the cutter.

For example, in one study that compared limbal and pars plana microincision vitrectomy for removal of congenital cataracts with primary intraocular lens implantation, more eyes had at least one intraoperative complication in the limbal group (40 eyes in 26 patients) than in the pars plana group (41 eyes in 30 patients). The most common intraoperative complications were iris aspiration, iris prolapse and iris injury. The study recommended use of the pars plana approach to ensure a lower incidence of complications.[1]

Some anterior segment surgeons, in fact, have promoted pars plana as a safer approach because it lets you efficiently remove vitreous from the anterior chamber without it; limbal infusion creates the pressure gradient that results in this advantage. This is safer than pulling vitreous anteriorly, which can potentially create vitreoretinal traction and retinal breaks. Limbal anterior vitrectomy can result in residual vitreous strands that can be challenging to remove and may even appear the day after surgery.

The pars plana approach allows the surgeon to use the vitreous cutter to remove remaining lens fragments in a much more efficient manner than can be achieved from the limbus. Dislocation of lens fragments is a serious issue because it increases risks of retinal detachments, secondary glaucoma and cystoid macular edema.[2]

When used with cataract surgery, pars plana vitrectomy's advantages have been documented in another study. Researchers looked at 335 eyes that had undergone anterior vitrectomy, and they concluded that a sutureless pars plana approach might be considered a safe and reliable solution for anterior segment surgeons in managing vitreous prolapse during anterior segment surgeries.[3]

All illustrations: Byron Wood

Figure 2. Keep the vitreous cutter and infusion source separate to reduce turbulence and endothelial trauma.

Point/Counterpoint: Dr. Maloney

• ***Source 2: Surgeons used to do coaxial vitrectomy with a single handpiece.*** In the old days, surgeons did vitrectomy with a combined infusion-cutting device. The irrigation sleeve was positioned over the aspiration-cutter, meaning that the handpiece hydrated the vitreous while it was simultaneously pulling vitreous into the cutter. Convection currents dispersed vitreous away from the cutting port and into the anterior chamber. Everyone now uses (or should use) bimanual vitrectomy instruments, with separated infusion and aspiration/cutting ports.

• ***Source 3: Surgeons tolerate leaky limbal wounds.*** Wound leaks bring vitreous forward, because vitreous moves to any area of low pressure. If you have leaky paracenteses around your bimanual instruments, vitreous will move into the anterior segment and to the wound. Make small watertight paracenteses for your vitrectomy probes.

Exceptions to Consider

If you can't get good access to the vitreous when entering the eye through the limbal port, you may want to use pars plana. Two classic situations are as follows:

• ***You have zonular dehiscence, and vitreous is coming forward around the zonule.*** You can't move the vitrectomy port around the zonule and into the posterior chamber. Pars plana vitrectomy is the preferred approach for the anterior segment surgeon at moments like these.

• ***After the IOL is already implanted, you discover a posterior capsule tear or create a posterior capsule tear.*** You can usually access the vitreous more easily by using the pars plana approach, rather than trying to work around the intraocular lens prosthesis.

Other than when anterior segment surgeons are dealing with exceptions such as these, they should consider limbal anterior vitrectomy to be their procedure of choice.

Risks of Pars Plana Vitrectomy

The primary risks of pars plana vitrectomy are retinal tear and detachment, which can occur in several ways. The surgeon can engage the vitreous base with the instrument, causing a dialysis or giant retinal tear. Alternatively, if the surgeon uses an MVR blade to make a scleral opening rather than using a trocar system, a knuckle of vitreous can prolapse through the incision. This can create retinal traction, particularly in the vitreous base area, and can become a scaffold on which fibrosis can develop. These responses can lead to a retinal detachment.

It's a rare anterior segment surgeon I know who can

(Continued on page 96)

Point/Counterpoint: Dr. Charles

Meanwhile, the principal advantage of limbal vitrectomy is the cataract surgeon's familiarity with the approach, although some argue that the limbal approach also reduces risk to the peripheral retina.

Minimize the Drawbacks

One of the purported drawbacks of a pars plana approach is the heightened risk of retinal damage. However, in my experience, you can minimize this risk with the proper technique (and this logic applies to whichever approach you choose). A pars plana approach is just as safe as the limbal approach with respect to the risk of retina damage if you keep critical principles in mind:

• ***Never use cellulose sponges to remove or test for vitreous.*** The sponges create unacceptable instantaneous intraoperative traction.

• ***Never apply aspiration to a vitreous cutter without first activating the cutting function.*** This prevents acute vitreoretinal traction from causing retinal tears.

• ***Never pull a vitreous cutter back while you're applying aspiration.*** This is important to prevent acute vitreoretinal traction from causing retinal tears. Remember: Use the opposite of I/A technique in these situations.

Besides following these principles, you'll always need to make sure you use the highest possible cut setting to reduce pulsatile vitreoretinal traction. Also, use the lowest effective flow rate (peristaltic pump) or vacuum (venturi) to decrease intraoperative traction and therefore the risk of iatrogenic retinal breaks. Using triamcinolone particulate marking will help you visualize better and judge how effectively you're performing the procedure.

Also, always make sure you place the infusion through a sideport—whether using a limbal or the pars plana route for the vitreous cutter. Never use a sleeve over the vitreous cutter for infusion. The vitreous cutter and infusion source must be separate to reduce the turbulence and the endothelial trauma I mentioned and to more effectively remove vitreous.

Remember that anterior vitrectomy is performed close to the vitreous base, the region of permanent and very strong vitreous adherence to the retina. Furthermore, keep in mind that the peripheral retina has 1/100th the tensile strength of the retina near the optic nerve.

Forego a Trocar Cannula

Another way to avoid common complications with pars plana anterior vitrectomy is to forego the use of a

(Continued on page 96)

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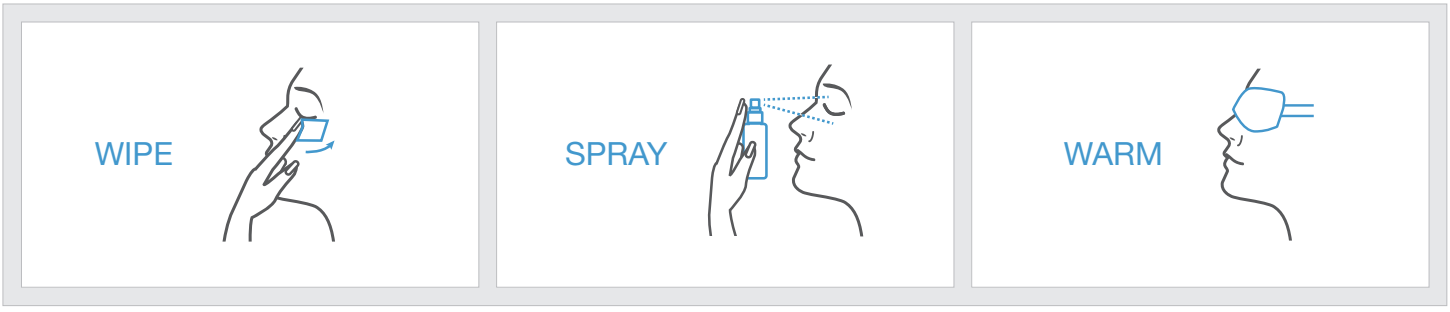

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The Ophthalmic Staffing Shortage

Christine Leonard, Associate Editor

Experts discuss solutions to the staffing shortage and offer strategies for recruiting and retaining staff.

The shortage of experienced ophthalmic staff seems to be the bane of practices nationwide. Thanks to a combination of low unemployment rates and lack of awareness of the job, the pool of staff and experienced ophthalmic technicians is quite small. Lynn Anderson, PhD, CEO of the International Joint Commission on Allied Health Personnel in Ophthalmology (IJCAHPO), says, "The reason JCAHPO was started in 1969 was that there weren't enough people in the profession to act as physician extenders. So there's a long history of not having enough technicians."

"All ophthalmologists are looking at the same short supply of people," says Richard Jahnle, MD, FAAO, president of Jahnle Eye in Havertown, Pennsylvania, and founding partner and board member of the Crozer-Keystone Surgery Center in Haverford.

Today, the problem is nationwide in almost every field, Dr. Anderson says. With the current unemployment rate in the health-care industry at a low of 2.3 percent as of August 2019,[1] jobseekers have their pick of employers. In the face of retirement, competing job offers and life changes, turnover among staff may seem inevitable. In this article, experts discuss the challenge of turnover and offer strategies for attracting and retaining good staff.

A Good Tech is Hard to Find

Erica Jahnle, the chief operating officer and practice administrator for Jahnle Eye, says it's almost impossible to find experienced technicians. "There are a number of ophthalmic medical technician programs in this

Patients Seen per Hour*

Number Seen	Allied Ophthalmic Personnel (%)	Ophthalmologist (%)
Less than one	2	1
1 to 2	5	3
3 to 5	46	34
6 to 10	28	50
11 to 15	6	6
More than 15	13	5

*All data courtesy of Association of Technical Personnel in Ophthalmology. Data includes both ATPO members and IJCAHPO certificants.[6]

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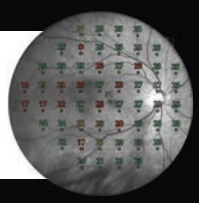

area. I know Camden County College and Philadelphia Community College have programs. But at least in this past year, to my understanding, they had very few students enrolled in those programs."

While a degree isn't necessary for a technician position, the educational experience is still very valuable. Ophthalmologists require highly specialized individuals to work with them. "It's not like most medical practices where you can just hire medical assistants or a nurse practitioner or a physician assistant," says Robert M. Kershner, MD, MS, FACS, professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College and president and CEO of Eye Laser Consulting Global in Palm Beach Gardens, Florida. "They don't know the eyes or understand the terminology the way we do. The only one who understands the eye as well as we do is an optometrist, and obviously, hiring an optometrist is going to cost a lot more money."

Most medical assistant programs train individuals in phlebotomy and taking blood pressure, but those skills aren't applicable to an ophthalmology practice. "Historically, we've accepted undertrained individuals who, for the most part, required in-house training, which takes a lot of time out of our practice and time away from staff," says Dr. Kershner.

He says ophthalmic training programs are the best-kept secret in the country. "There are only about 30 programs in the United States that are certified by the International Council of Accreditation for Allied Ophthalmic Education Programs that train people to become ophthalmic technicians or technologists.[2] For certified ophthalmic technologists, there are only three accredited programs in the nation, including the one I established. That's pretty sad. We're obviously making a dent, but we can't possibly train enough people to meet the need."

Dr. Kershner's program at Palm Beach State College launched in 2012. It offers an Associate of Science degree that includes two clinical rotations in dozens of externship sites. Typically, only 15 students are accepted each year. The Bascom Palmer Eye Institute usually hires most of the program graduates.

Average Compensation of Certified Personnel

	Hourly	Annual Salary
Certified Ophthalmic Assistant (COA)	$22.90	$59,773
Certified Ophthalmic Technician (COT)	$25.90	$66,008
Certified Ophthalmic Medical Technologist (COMT)	$29.50	$79,954

While the job outlook for technicians is good, that's only because the supply of technicians lags far behind the demand. "The need for techs in this profession is significant, with medical assisting listed with a projected growth rate of 29 percent from 2016 to 2026," says Dr. Anderson, citing the Bureau of Labor Statistics job outlook projection.[3] The BLS considers this growth rate to be much faster than average for all occupations, due to the aging baby-boom population and the accompanying increase in demand for preventive medical services.[3]

Additionally, the 2019 update on the complexities of physician supply and demand and projected numbers from 2017 to 2032 for the Association of American Medical Colleges finds that there won't be enough new doctors to care for the growing numbers of patients as the current generation of older doctors retires.[4]

"Every ophthalmologist I know is already working to get as many patients as they can to make ends meet, so they're not going to be able to see even more patients or do much of anything else," Dr. Kershner says. "They'll need ophthalmic techs trained to do the entire exam so the doctor can just sign off on it. That frees the doctor to do what only the doctor can do, and that's surgery and laser. We have an aging population and an increased demand for ophthalmic services. We need to have more personnel as physician extenders."

Programs and Certification

Certification serves as a benchmark for competency, performance standards and up-to-date knowledge, according to IJCAHPO's criteria for certification. Steven Dewey, MD, in practice at Colorado Springs Eye Clinic, says, "Our field is changing so rapidly. It's difficult to stay on top of all of the advances and changes. We definitely prefer that techs be certified, and the pay scale reflects that. They get rewarded for their additional training and maintenance of certification."

Likewise, degree programs offer consistency in preparation, explains Anthony R. Garand, executive director of the Bascom Palmer Eye Institute. "Too often in the practice setting, the demand of the daily workflow and the needs of the practice limit training and teaching capability. Also keep in mind that good technicians aren't necessarily good teachers."

Furthermore, Mr. Garand notes that program-trained technicians tend to have a greater comfort level with testing and the certification process due to the academic nature of their training program, and they're ready to take the certification exams earlier than in-house-trained technicians. He says, "The bottom line is that a certified technician has an advantage and is better prepared. Training on-site is time-consuming and not a guarantee of success. In-house training of staff requires significant internal motivation."

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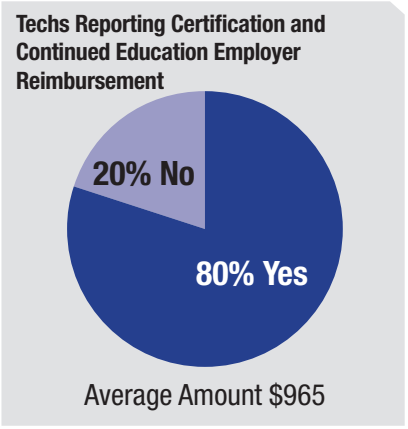
IJCAHPO is the governing organization for continuing education and professional certification for ophthalmic medical personnel. Certification is examination-based and candidates must hold a high school diploma or the equivalent and have completed either an accredited formal clinical training program or some combination of accredited formal training program or independent home study and work experience.

Ophthalmic credentials include Certified Ophthalmic Assistant (COA), Certified Ophthalmic Technician (COT) and Certified Ophthalmic Medical Technologist (COMT). COAs have basic, entry-level knowledge with about one year of study. COTs have more skills and can also train to take tonometry and measure refraction. The COMT is the highest level of certification, indicating that an individual has been trained on all equipment in the office, can oversee staff and can even assist the ophthalmologist in surgery. A 2008 comparative impact study found that, compared to noncertified personnel, the employment of certified ophthalmic medical personnel enhances and increases practice quality and productivity.[5]

"The ideal assistant for an ophthalmologist would be a certified ophthalmic medical technologist," Dr. Kershner says. "My experience has been that once ophthalmic practices are introduced to highly-trained individuals and work with them, they can't get enough."

Encouraging certification benefits practices in the long run while offering technicians avenues for personal growth. "Certification justifies a higher salary and makes an employee more competitive for hiring," observes Mr. Garand. The 2017 Salary Survey from the Association of Technical Personnel in Ophthalmology puts Certified Ophthalmic Assistants at around $21.09 an hour and non-certified at around $19.55 an hour.[6] Gaining another level of certification can boost a technician's annual salary by as much as $10,000.[6]

Educational Reimbursement



In-House Training

Most doctors agree that hiring certified ophthalmic staff is preferable to expending resources for training, but much of the time it's just not possible. However, "Nobody's telling you that you can't hire technicians without certification, or that they can't do x, y and z without certification," says Becky Reitinger, president of Reitinger & Associates, an ophthalmic consulting firm in Eugene, Oregon.

Certain subspecialties, such as retina and oculoplastics, don't need certification for some tasks, but instead can just be trained. Certification is geared more toward general ophthalmology and teaches skills like refracting.

For Dr. Dewey, a medical background is a must for prospective techs. His practice has hired certified medical assistants who didn't know much about eyes but came with an interest in learning. He assisted with their training. "I don't recall the last time we took somebody who had no medical background and trained them to become an ophthalmic tech," he notes.

Dr. Jahnle says his practice's training program is like an internship or an apprenticeship, where the new technicians learn on the job. Jahnle Eye's clinical coordinator is JCAHPO-certified and is the main trainer for the new technicians. Additionally, a JCAHPO trainer comes to the office for a boot-camp-style training for the inexperienced hires. "This is kind of an extraordinary circumstance for us, because we hired two new doctors and had to hire a big group of technicians all at once," says Ms. Jahnle. "This was a convenient way to add to their training."

Dr. Kershner sees an advantage in having someone experienced with the eye. Though hiring a certified ophthalmic technician costs more than hiring an inexperienced person, Dr. Kershner says it's less risky and worth the investment. He says an in-house-trained technician may leave your practice for someone who's paying a dollar more per hour than you are, after you've invested time and money in their training and experience. If you hire a person with training and they leave to work elsewhere, you haven't lost anything except the person. "For what you pay an ophthalmic tech, you can see a lot more patients and do a lot more," he says. "A highly trained individual with their own skillset who doesn't need supervision can make you a lot more money because they can do things to alleviate the burden on the doctor."

The Challenge of Turnover

Turnover brings in new people and new energy, which can refresh a practice, says John Pinto, ophthalmic practice management consultant and president of J. Pinto & Associates in San Diego. But it's costly. "We spend about thirty cents of every dollar we take in on staffing costs, so there's a lot at stake," he says. "Getting it right can make big, positive differences in profitability, and doing it poorly can really kill a practice's financial performance. It's really impossible to place too much importance on what you're doing in this area."

Too much turnover is disruptive to the practice, says Dr. Kershner. "Pa-

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tients love to see the same person when they come each time. They obviously bond with your techs."

Professional, qualified personnel are in high demand, and competing offers from private practices are strong draws, says Mr. Garand. Dr. Kershner adds that private practices generally have higher starting salaries, better hours, and more opportunities for growth and responsibility than hospitals.

Despite the state of staffing, Dr. Jahnle remains optimistic. Employees leave for plenty of other reasons besides money. Sometimes a job just isn't the right fit. "At the beginning, we try to explain what the job's going to be like, but they don't know until they actually do it," he says. "Occasionally we have people who work for a very short time and decide it's not what they thought it was going to be, or it was too busy. But most people who stay on past the first few months end up staying for a while." In some cases, techs just take the job temporarily on their way to more advanced schooling.

However, perhaps the biggest factor influencing turnover is job dissatisfaction. An internal IJCAHPO survey of technicians found that unhappiness with the employer was the number one reason for leaving a job. "A lot of doctors say, if I get them certified they'll leave or if somebody offers one dollar more across the street they'll leave," says Dr. Anderson. "And you know, to some degree that's true, but actually it's more likely that they're not happy working there anyway."

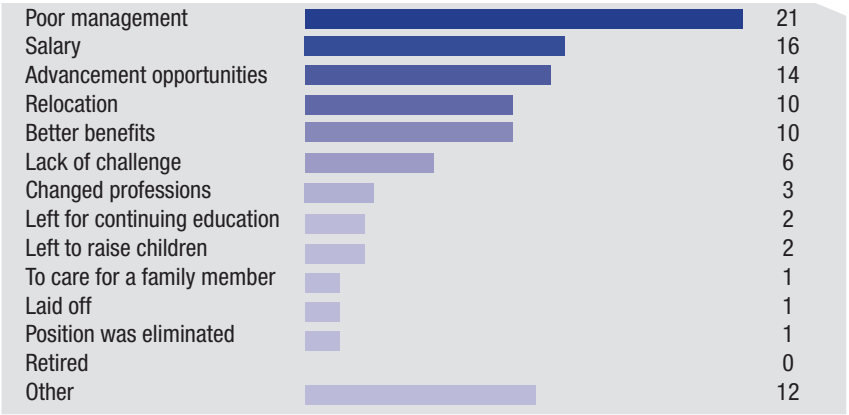
Mr. Pinto identifies a diffuse feeling of low morale as the causative factor in job dissatisfaction. "The doctor's respect for the staff can bring the morale level up to around seven or eight out of 10 points," Mr. Pinto explains, citing a proprietary tool he and Corinne Wohl, MHSA, COE, ophthalmic practice management consultant and president of C. Wohl & Associates in San Diego, use to measure staff morale. "The most common reason for low morale, when you dig a little deeper and ask staff, is some aspect of doctor behavior.

"This could range from 'The doctor didn't say hello to me in the morning when she came in,' or 'The doctor's delayed in getting dictation off to me,' all the way up to just frankly being rude and insecure or saying one thing and doing another or blowing staff off," he says. In their experience, a low morale level often correlates with a high turnover rate.

"This doesn't require bringing in muffins every Friday morning," Mr. Pinto says. "What you don't want to do is leave through the back door every evening and over your shoulder say, 'Thanks, guys. It was a great day.' Instead, throughout the course of the day, you want to catch people doing good things and cite them for that specifically and publicly."

Ms. Wohl says adding workplace enjoyment or "formalizing fun" is key to raising staff morale. "Take time on a regular basis (at least monthly) to show appreciation for the staff and have some fun in the practice" she says. "A game of bingo, via email, or solving trivia quizzes are small ways to incorporate fun without impacting patient care." Some other activities might include celebrating holidays, dressing up for Halloween—yes, even the doctor—or a barbecue. "Ultimately, we're talking about teambuilding and showing that the practice cares and appreciates its employees. Anything you can do that puts a little break in the day that's cheerful and positive for employees will help team spirit and get them engaged at a different level than being only work-focused."

Reasons for Leaving (percentage)



How to Find a Tech

Experts are noticing a trend in today's technician job applicants that differs from technicians hired 20 or 30 years ago. "We have a lot of people here that have been with us for decades," says Ms. Jahnle. "You can't even measure how valuable that is for us. But it's a different kind of applicant pool out there right now."

In Mr. Garand's experience at Bascom Palmer, "the newer employees tend to look at hourly salaries and short-term rather than long-term benefits." Ms. Reitinger agrees, saying that "the younger generation doesn't seem to want to commit to long-term jobs. They want a job for six months or a year, and most of the ophthalmology clients that I have say technicians are just learning their job by then. So that doesn't really work out well for them."

It's important to know what today's job applicants are looking for, as well as how they're searching for jobs. Here are some pearls for finding good staff and keeping them in your practice.

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• ***Consider the 'what's in it for me' factor.*** That's what candidates are looking for today, says Ms. Galasso. With the low unemployment rate and scarcity of technicians, it's more important than ever for practices to make their job offers attractive. "Today, it's all about 'why should I not miss out on this employment opportunity?'" she says.

"Consider all of the things that attract any candidate in any market, which are incentives, competitive compensation and great perks," Ms. Galasso continues. "If I've worked for a practice for 15 years and have five weeks of paid time off now, and you only offer two weeks, it's going to be a tough sell for me. So you're looking for all the ways you can market why it's a great opportunity."

"Talking about what the work environment is like, and having a lot of great, long-standing employees shows that your practice is a great place and people want to stay there," says Ms. Reitinger. "Everyone in general is more focused on work environment today, not just this current generation."

Health-care insurance is another important factor in a candidate's decision to change jobs, explains Ms. Galasso. "They'll always want to know what their monthly out-of-pocket expense will be relative to what they have now," she says. "Candidates who've been somewhere for five or more years likely have health-care insurance that works for them, a retirement plan or profit sharing, level-up paid time off, and other perks that come with tenure—some type of investment in them as a long-term employee."

"If it's been a long time since your practice has performed a local market salary survey, it's worth the effort," says Ms. Wohl. "You want to be offering fair and competitive wages in order to attract qualified, talented staff."

• ***Determine your applicant's goals.*** Ms. Galasso says a 10-minute phone interview to prequalify candidates will save you time. Ask what

they're looking for in an employer or when they'd be available to start. If their goals don't match what you can offer, don't waste your time.

• ***Market your practice.*** The general marketing of your practice also impacts your HR, explains Ms. Reitinger. If your practice is perceived as a really cool place to work or has a strong reputation among staff people, then people will be more excited to apply. Consider putting a "Careers" section on your practice website.

• ***Keep online job postings short.*** Ms. Galasso says it's important to have attention-grabbing headlines that are easy to understand. "Differentiate your ad with a catchy introduction, something that looks a bit different from everyone else's," she advises. Job applicants will skip a wall of text, so Ms. Galasso no longer advocates adding full job descriptions in the posting. "Use bullet points for listing key core competencies that someone would need to fulfill the role, then provide a job description when you decide to interview them," Ms. Galasso explains. "Most people are able to do their job effectively because they have skills, but moreover because they have core competencies that are both foundational and scalable."

• ***Initiate contact within 48 hours.*** The low unemployment rate means your applicant is likely talking to multiple prospective employers. Connecting with the candidate right away is important. Ms. Galasso recommends a 48-hour window, either by email or phone. You don't have to hire that first person, she says, but if you wait for another week, you're going to lose that candidate.

• ***Don't hire too fast.*** While it's important to make that initial contact, take your time and make sure the candidate is a good fit. Ms. Reitinger notes that in this environment, practices feel pressured to hire right away. "You've got to know this is a good fit, because firing or dealing with a difficult employee is much more painful than not having one," she says.

Benefits Most Important to ATPO Technicians (percentage)*

*Multiple responses allowed

• ***Try shadowing.*** This allows the candidate to get to know the practice in an informal environment and see if it's a good fit for them. It also gives your current employees a chance to get to know their prospective colleagues, says Ms. Reitinger.

• ***Have multiple staff members interview the finalists.*** "It can be a serious mistake for just the office manager to interview a candidate, hire them on the spot, and then introduce them to the colleagues they're going to be working with the next week," says Mr. Pinto. "It's important, for example, if you're hiring a prospective new tech, that all the techs in the department have a chance to meet that finalist before the hirers make the decision."

• ***Look for personality.*** "It's worth it to hire someone with a good personality," says Ms. Jahnle. "We can always teach them the technical skills, but it's much harder to teach someone to be patient and kind."

• ***Look for adaptability.*** The medical field changes rapidly, and adaptability is especially important in the case of office staff, notes Ms. Jahnle. "The codes we use are changing," she says. "Medicare fees are changing. Electronic medical records are changing. So candidates have to be very open to change and learning new things all the time. I think if they're not comfortable with that, it's probably not a good role for them."

How to Keep a Tech

Whether a person is newly hired or has been with your practice for years, there are certain things you can do to help retain them.

• ***Create opportunities for growth.*** Practices need to help employees understand that they're growing, even if they're doing similar things, says Ms. Reitinger. "It seems to be a generational thing," she says. "Today, applicants feel they need to move on to grow."

By helping people take ownership for different aspects of their job, practices can improve retention. "When people

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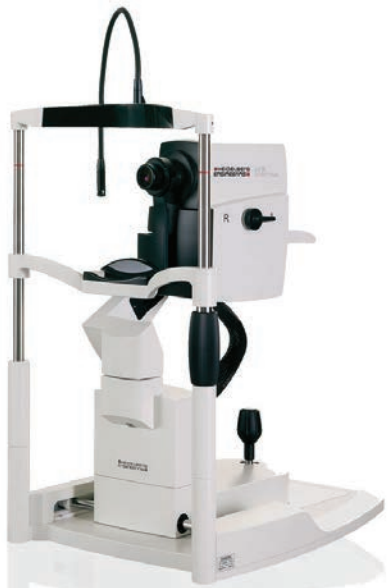

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are too much in a box, it can feel like a dead end," Ms. Reitinger says. "If you're good in the phone room, we're not going to let you out because you're so good! Instead, find out if they'd like to do something different and let them learn a new skill. The offices that are more willing to follow people through their progression of learning keep people a lot longer."

• ***Check your on-boarding process.*** Ms. Wohl says a well-established onboarding process can improve employee retention, especially during the first few years of employment. Having a coordinated, thoughtful training period with standards to meet enables an employee to begin with a strong footing. "Designate a specific person to do the training, not someone who just happened to be available that day," she says. "Choose someone you think will do a great job so they'll train the new person the way management wants them trained.

"You should have a formal onboarding checklist that includes all the job functions so you know training has been completed thoroughly," Ms. Wohl continues. "This helps the new employees become confident more quickly than if it's done in an disorganized fashion. The management team is responsible for preparing a current position description and onboarding checklists so the expectations for new hires are clear to all."

• ***Recognize a job well-done.*** Dr. Dewey finds that good technicians who take their time with patients make the day flow better and have improved his own patient interactions. "Ophthalmology is a peculiar field because we're relying upon the patient to give us their own perspective on how things are working," Dr. Dewey says. "It's obviously very difficult to separate our own biases from what the patient is telling us. Finding a tech who can objectively listen to a patient's very subjective issues is a challenge, so when you find individuals who can really help the patient with what they're going through, and help them understand what needs to happen, you really need to make sure those employees are rewarded."

• ***Take your charm pills.*** Mr. Pinto recommends treating your employees like your patients, or as if they were volunteers. "What would you do if you had a volunteer in your office?" he asks. "You might go to the break room and get them a cup of coffee. You might say at some point, 'We really appreciate your being here. You mean a lot to us. Thanks for putting in the time.'"

Dr. Kershner agrees. "Techs don't recognize their value based on how much they're getting paid but by how well they're treated," he says. "They have to feel that they're appreciated and respected and that you're helping advance their skills."

• ***Show them they're making a difference.*** Dr. Jahnle says that most people in the medical assisting field want to help people. "They like the idea that a patient comes in and has a problem and they're involved in helping the person," he says. "So if you can show them that they're actually helping people, I think that's what makes them stay."

Start Your Own Program

A 2016 qualitative case study found that establishing formal training programs was part of an important strategy for supplying a skilled, qualified ophthalmic workforce to meet the future demands of ophthalmic patient care.[7] Likewise, a 2011 comparative analysis surveying ophthalmologists identified trained ophthalmic medical personnel as both a need and a means of increasing productivity.[8]

"There's a tremendous lack of awareness of this profession by the public and people seeking a job," Dr. Anderson says. She says that the shortage of degreed and certified technicians stems in part from the traditionally nonacademic nature of the job, since most employees can be trained on the job.

Dr. Jahnle says more training programs would benefit the ophthalmology community. "It'd be great if the ophthalmologists could work together," he says. "Then everybody who graduates from the program could work in somebody's office. But it's hard to do that."

The 30 ophthalmic technician programs in the United States are sprinkled among just 19 states and the District of Columbia. Only seven programs offer Associate degrees, and nine are still in the process of accreditation.[2] North Carolina has five programs and Texas seven, but most states with programs have only one or two, which makes accessing these programs an additional obstacle.

"We need to encourage local ophthalmologists to start and support a training program," Dr. Anderson says. "We need support by ophthalmologists at all levels for technicians—mentoring, compensation, education and training, certification and more."

To help address the shortage, experts say you can express the need for trained technicians to local academic institutions, help develop a curriculum for schools that are interested, become a faculty member in a training program, help a school apply for accreditation and be ready to hire graduates when they come out.[9] Your next technician could be easier to find than you think. REVIEW

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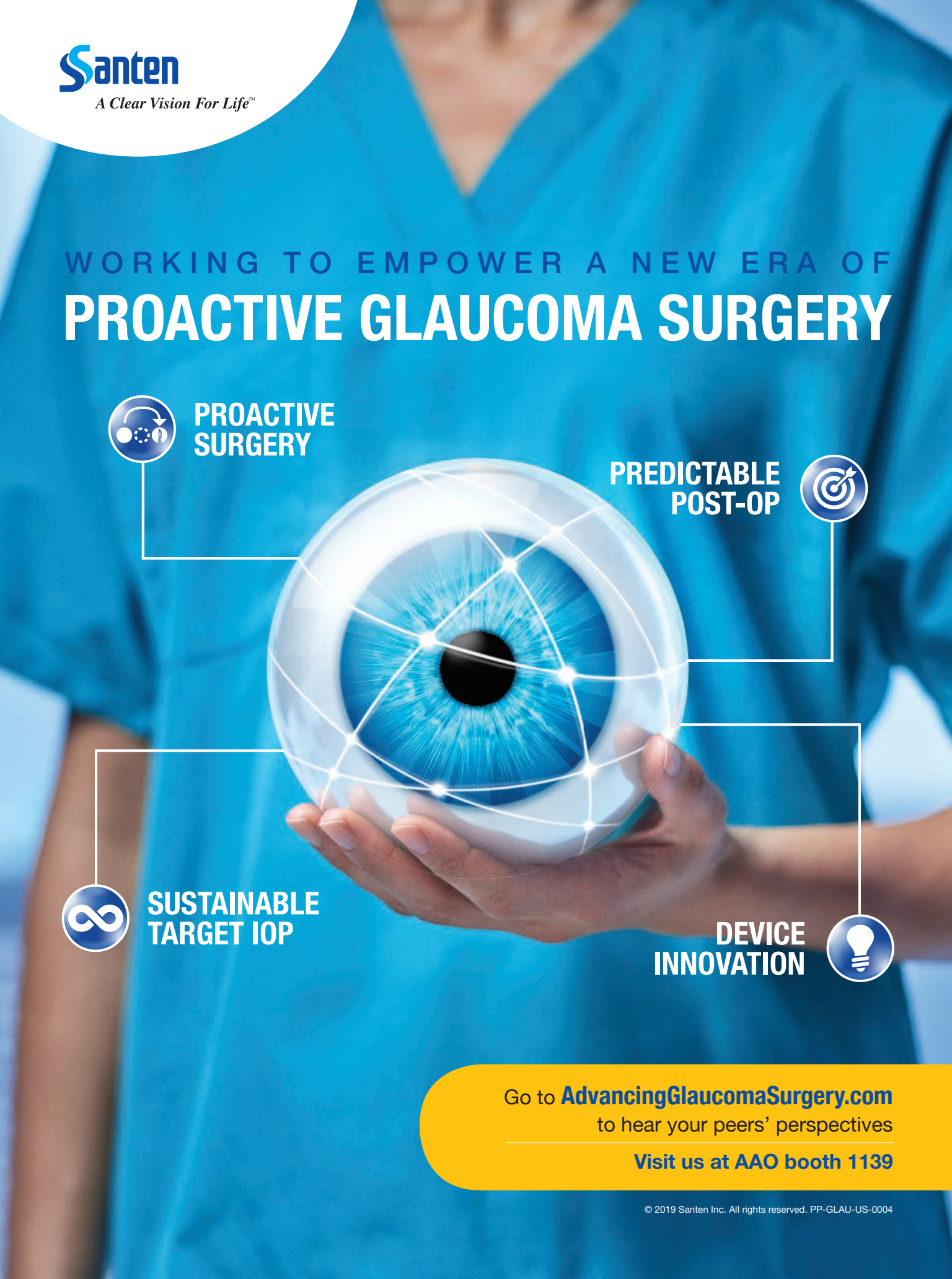

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How to Break Down The Nucleus

Michelle Stephenson, Contributing Editor

Leading surgeons share their best tips for residents faced with complex cataract cases.

Since the advent of phacoemulsification, surgeons have been developing innovative ways to break up and remove the cataract. Some like horizontal chopping, while others prefer techniques like divide-and-conquer. Here, cataract surgeons describe their favorite techniques, as well as how they adjust these approaches based on the density of the cataract.

Horizontal Quick Chop

Sumit (Sam) Garg, MD, who is in practice in Irvine, California, primarily uses a horizontal quick-chop technique for nuclear disassembly. He first uses the phaco probe to impale the nucleus. Then, he uses a Seibel chopper to go around the equator of the lens and chop the nucleus in half, then into quarters or sixths, depending on the density of the lens.

"That's my go-to," says Dr. Garg. "When I graduated from training, I was very comfortable with stop-and-chop, which I think is still a very useful technique for difficult lenses. And, sometimes if the lens is really tough, I'll go back to stop-and-chop, which involves using the phaco probe to create a groove centrally, and then cracking that groove in half. Then, you move to chop. But, at that point, you've already divided the nucleus into two, so the chopping becomes a little easier."

He adds that one of the advantages of the horizontal quick-chop technique is that it delivers less phaco energy into the eye. "Additionally, in my experience, it's a little more efficient with respect to time, so I'm able to accomplish nuclear disassembly in just a few seconds," Dr. Garg says. "However, surgeons who use divide-and-conquer can be really fast, too, so I think it's sort of a wash at the end of the day. But I learned chopping and, to me, chopping makes a lot more sense than burrowing out or bowling out a cataract. And so, if you can break up a cataract mechanically using less energy and fluid, that intuitively makes sense to me. Also, I'm a big fan of using my second instrument to help move things around and bring pieces closer to the phaco tip and trying to keep the phaco tip near the center of the eye for most of the case."

Divide-and-Conquer

James Davison, MD, who is in practice in Des Moines, Iowa, uses different techniques for different types of cataracts. He uses the LOCS III grading system, which was devel-

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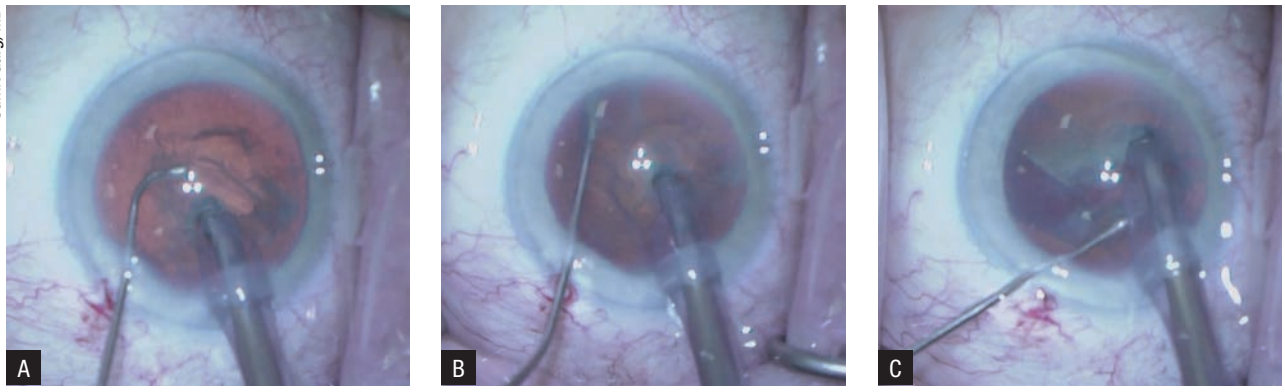

Figure 1. For Dr. Garg's horizontal chop technique, (A) impale the nucleus with the phaco tip, (B) place the chopper at the equator of the nucleus, (C) bring the chopper and phaco tip together to achieve fracture of nucleus.

oped in 1993 by Leo Chylack, MD, at Harvard.[1] This system grades cataracts on nuclear opalescence (NO; scale from 0.1 to 6.9), nuclear color (NC; scale from 0.1 to 6.9), cortical spoking and posterior subcapsular area (P). "If the NO and the NC are 3.6 or less, then we know the nucleus is soft enough to use an Akahoshi prechopper to divide the lens into quarters and then remove it," Dr. Davison explains.

For medium-firm lenses (LOCS III NO and NC 3.7 to 3.8), he uses a divide-and-conquer technique. "We like to use a Connor wand for these because some of these lenses are a little bit softer, and the cyclodialysis spatula will sink into the nuclear substance as it's pushed against it when tearing the posterior nuclear plate," explains Dr. Davison. "The Connor wand will give you a little more vertical surface area to push on the face of the nucleus to crack it. So, we use the 45-degree Balanced Tip to sculpt our grooves, then we use the Connor wand to break the nucleus into quarters, and then we shave away the remaining firm corners, all in the sculpt setting. So, we remove as much of the hard material as we can while the nucleus is in the capsular bag, and then we turn the machine to epinucleus or quadrant removal settings and bring the relatively thin two-dimensional pieces into the empty nuclear bowl to remove them."

A Connor wand isn't needed for firmer cataracts (LOCS III NO and NC 3.9 or higher). "We use a cyclodialysis spatula that's been modified from 0.5-mm to 0.35-mm diameter," Dr. Davison says. "It seems to be just right for cracking the posterior plate and maneuvering the nucleus and then its fragments." Surgeons say a dispersive viscoeleastic helps facilitate these maneuvers.

When the chop technique was introduced in 1994, Dr. Davison performed it using several different instruments. However, after trying several variations, he found that the corneas were just not as clear with that technique. "I got some Descemet's folds, but I hardly ever get them with any of the divide-and-conquer techniques," he says. "I found that my endothelial cell loss rate for relatively hard cataracts was 2.7 percent.[2] So, for me and my skill set, the way I've been trained, and the way I've worked, it's been better for me and better for the patients to use the divide-and-conquer techniques. The chop technique typically doesn't require as much ultrasonic energy from the machine, but it depends on higher levels of vacuum to aspirate nuclear fragments, so you can get really low ultrasonic energy use times and amounts with that technique, but you have to bring up the piece that you break off into the iris plane and anterior chamber to remove it. You can get a little more generous and keep it away from the cornea in the later pieces that you break off and aspirate, but for the first pieces, you have to bring them into the anterior chamber to remove them. Although it's a little faster and has lower energy consumption measured on the machine, the corneas look better if I just do the divide-and-conquer technique."

Horizontal and Vertical Chop

Richard Hoffman, MD, who practices in Eugene, Oregon, performs bimanual phaco and uses a chopping technique for nuclear disassembly. He performs horizontal chopping for softer lenses and vertical chopping for denser lenses. "I basically hydrodissect and hydrodelineate the lens into an endonucleus, an epinucleus and the cortex," Dr. Hoffman explains. "Then, I remove the endonucleus using a chopping technique and use the epinucleus as a buffer between the phaco needle and the posterior capsule. Next, I remove the epinucleus and then the cortex. However, many times, as I'm removing the epinucleus, if I've done cortical cleaving hydrodissection, the cortex comes with the epinucleus."

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Use of corticosteroids may result in posterior subcapsular cataract formation.

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

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

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

Fungal infections 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.

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

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

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

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

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

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

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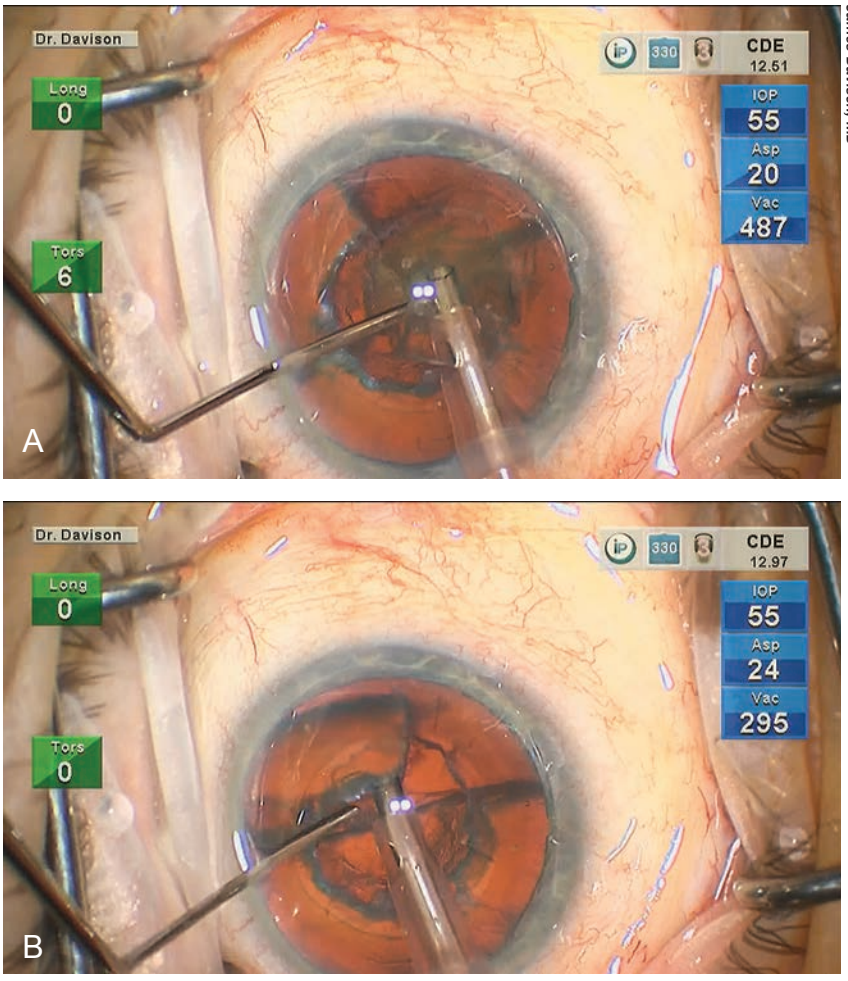
Dr. Hoffman uses irrigating choppers and has moved from 20-gauge to 21-gauge because the phaco needles are now 21-gauge. "It's a 21-gauge irrigator with a chopping element on the bottom end of the irrigator," he adds.

Dr. Hoffman notes that there are advantages to a bimanual technique. "We prefer that technique," he says. "When new doctors come into our practice and switch from coaxial to bimanual, they seem to like it. It is important to remember that the smaller the incision, the less induced astigmatism, and the safer the eye is from blunt trauma. Another advantage of bimanual is its I/A. If you're performing bimanual phaco, it's very easy to use bimanual I/A, and that makes removal of the cortex much easier than doing it coaxially."

Additionally, he says that a bimanual technique is advantageous in certain challenging cases where you might not want to rotate the lens. "By doing the procedure bimanually, you have access to the lens from two different directions," Dr. Hoffman says, "so you can actually switch the phaco handpiece and the irrigator between the incisions. It's really nice for posterior polar cataracts and for IFIS patients because you can have infusion from your second handpiece kept above the level of the iris. This results in a lot less billowing of the iris."



James Davison, MD

Figure 2. In Dr. Davison's technique, (A) the nuclear fragment is held within the central bowl as it's being emulsified and (B) the second quadrant is ready to be accessed and drawn into the bowl for removal.

Pearls

Dr. Garg advises surgeons to use different techniques for different types of cataracts. "Some cataracts don't require as much chopping," he notes. "I think it's important for people to know about other possible techniques, but also to have one go-to that they feel most comfortable doing for the majority of their cases. If you have that repetition, then you get really good at that one technique."

He adds that it is important to remember to protect the cornea, especially in cases involving dense lenses. Dr. Garg uses a dispersive viscoelastic to make sure that the endothelium stays protected. "Then, you can always use the same viscoelastic in the bag if the bag is floppy," he says. "If you're unable to get pieces to move around, you can always put a little viscoelastic into the capsular bag to help keep it stretched a little bit. Then, use your second instrument to move pieces toward you or move a piece that's stuck. Often, we go after those with our phaco handpiece, but, when you're vacuuming, even if you're not in phaco, you have a higher chance of damaging the capsular bag than you do with a blunt instrument."

Dr. Davison also believes that all of the current techniques are good choices, so surgeons should choose the technique they're most comfortable with, as long as they take care when working on the last section of nucleus and use enough viscoelastic. "I put in more before the last quadrant if the lenses are firm because I think there's probably more damage done to the last quadrant than anything else," he says. "You use the shell of the nucleus that's remaining to protect the posterior capsule while

you're breaking up the fragment that you're working on. But, when you're down to the last quadrant, there's nothing to protect the posterior capsule. The surgeon, fearing capsule disruption or capsule aspiration, moves everything closer to the cornea in the iris plane. So, you are almost always very close to the cornea when you're taking out that last piece. And if it's a big, hard piece, you can really rattle it around and bang up the cornea when you do that. This is why it's important to add more [viscoelastic] before removing the fourth quadrant."

The Future

Dr. Garg notes that companies and surgeons are exploring techniques that don't rely on phaco to remove cataracts. "The miLoop (Carl Zeiss Meditec) is helpful to remove really dense lenses, and some people advocate using that for all cases," he says.

A study published earlier this year (albeit by researchers with financial interests in the miLoop) found that microinterventional endocapsular fragmentation with the manual, disposable miLoop device provided consistent, ultrasound-free, full-thickness nucleus disassembly.[3]

This prospective, single-masked, multisurgeon, interventional, randomized controlled trial was conducted to assess the safety and efficacy of microinterventional endocapsular nuclear fragmentation in moderate to severe cataracts. It included 101 eyes of 101 patients with grade 3 to 4+ nuclear cataracts. Eyes were randomized to torsional phacoemulsification alone (controls) or torsional phacoemulsification with adjunctive endocapsular nuclear fragmentation using a miLoop. Outcome measures included phaco efficiency as measured by ultrasound energy (cumulative dispersed energy), fluidics requirements (total irrigation fluid used) and the incidence of intraoperative and postoperative complications.

For this study, only high-grade advanced cataracts were enrolled. More than 85 percent of eyes in both groups had a baseline best-corrected visual acuity of 20/200 or worse. Mean CDE was 53 percent higher in controls (32.8 ±24.9 vs 21.4 ±13.1) than in patients in the miLoop group. Endothelial cell loss after surgery was low and was similar between the groups (7 to 8 percent).

One month postoperatively, best-corrected visual acuity averaged 20/27 Snellen in the miLoop eyes and 20/24 in control eyes. Intraoperative and postoperative complication rates were comparable between the groups; however, there was a trend toward a lower rate of capsular tear during the phaco portion of the procedure with miLoop-assisted phaco (7.5 percent) compared with standard phaco (10.4 percent). One eye in the miLoop-assisted group experienced a capsular tear related to the intraocular lens inserter when implanting the intraocular lens.

Dr. Garg notes, however, that it will be difficult to stop relying on phaco for cataract procedures. "There's some thought that some of the newer technologies may be able to move us away from phaco," he says, "but something's going to have to be really dramatic and really efficient to move us in that direction." REVIEW

Dr. Garg consults for Johnson & Johnson Vision and Dr. Davison consults for Alcon. Dr. Hoffman has no financial interest in any product discussed.

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Glues and Sealants in Tube Shunt Surgery

Using glue instead of stitches can sometimes be beneficial for both the patient and the surgeon.

Nathan M. Radcliffe, MD, New York City

Glaucoma surgery is always evolving. One of the ways it's changed in recent years is that more surgeons have begun using glues and sealants instead of sutures to close wounds and cover tubes during surgery. However, it's become a part of glaucoma surgical dogma that when performing surgery, sutures should be accepted as the standard of care. That may be part of the reason many surgeons have been hesitant to switch to glues and sealants. If suturing works, why switch to a different approach?

Here, I'd like to share some of my experience moving from sutures to glues when performing tube shunt surgery, and explain why I believe it's an option every glaucoma surgeon should consider.

Pros and Cons

If you take a step back, you'll see that sutures have some limitations. In fact, in some situations, sutures can be sub-optimal and even dangerous. To take a stitch, you have to pierce the skin, or cornea or sclera, causing a small amount of damage—that's how sutures maintain purchase. Doing so causes inflammation and often causes bleeding, and it creates a nidus for infection. Sutures can also cause the patient to have a foreign-body sensation postop.

Now that I've been performing tube shunt surgery using glue instead of stitches for several years, I can list several advantages to using glue in this situation, beyond just avoiding infection:

• ***Less time in the OR.*** In my experience, using glue to complete this type of surgery saves operating room time. In addition to efficiency, that's important for patient safety because a shorter surgery is often a safer surgery. The longer someone is in surgery, the higher the probability of something unintended happening.

• ***Patients are more comfortable postoperatively.*** In addition, their eyes look whiter and quieter sooner.

• ***Using glue reduces the need for postoperative steroids.*** I've found that eyes that have been glued have a lower requirement for postoperative steroid. The patients are comfortable because there's no foreign body reaction associated with glue. In contrast, vicryl sutures are pro-inflammatory, which will cause you to use more steroid.

• ***Complications and reoperation rates are similar to those of sutured surgery.*** We recently published a retrospective case series study designed to evaluate the safety and efficacy profile of 122 Ahmed glaucoma valve implantations in 99 patients performed using Tisseel fibrin sealant instead of sutures.[1] Eighteen eyes received the tube only; 46 also underwent cataract extraction; 35 had adjunctive endoscopic cyclophotocoagulation; and 23 had the valve with cataract surgery and ECP. The rates of re-operation and complications in our study were very similar to (if not lower than) those seen in other studies such as the Ahmed Baerveldt Comparison study and the Ahmed vs. Baerveldt study, which involved surgeries done using sutures.

• ***Glue rarely fails unexpectedly.*** If all of the construction is done appropriately, you won't need to be re-operating because of glue failure. I've seen that happen once or twice—but I've also seen that happen with sutured

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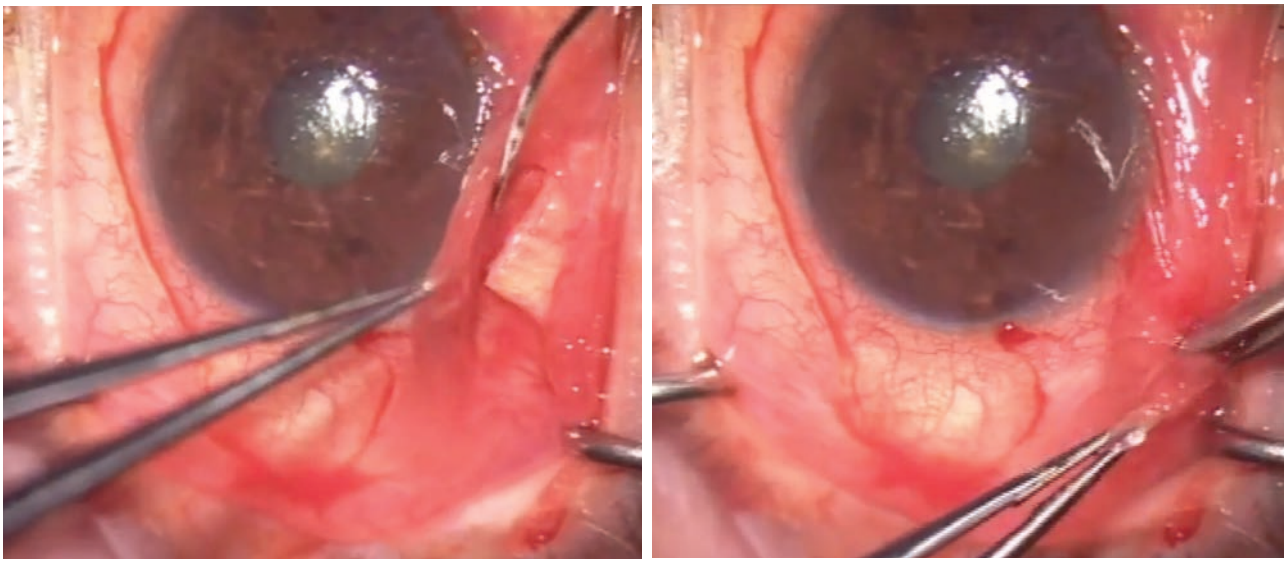

An Ahmed valve is implanted using glue instead of stitches. A conjunctival peritomy has been made about 5 mm posterior to the limbus to allow tension-free wound closure. After the valve and tube are put in place, the tube is covered with a patch graft; then everything is thoroughly dried to ensure that the glue will adhere to the tissue. The glue is then applied (above, left), and the tissue is held together as the glue seals the wound (above, right).

wounds. I don't think there's a big difference in this respect, especially if you follow all of the suggestions I've outlined below.

Limitations of this approach would include:

• ***Cost.*** Sutures are sometimes (but not always) less expensive than glue. Ultimately, the cost will depend on which suture material is being used and how your facility handles the purchase of glue.

It's definitely important for the surgeon to have a sense of how much the ASC or OR is paying and getting reimbursed for glue—as well as any other surgical tools being used. You should work within those parameters and do whatever makes the most sense in that situation.

• ***Applying glue requires working quickly.*** Because glue will harden, timing matters. That's not an issue when using stitches.

• ***Glue may not work in every situation.*** For example, it won't work if the wound is under tension; sutures may have a greater tensile strength. If you do use glue and it doesn't work, you'll have to add a stitch or two, making twice the work.

• ***The patient may be able to feel the presence of the glue on the ocular surface.*** This is possible; however, sutures will always be more irritating than glue.

• ***There's a small learning curve.*** The doctor and technician both need to become accustomed to mixing and applying the glue during surgery. However, there are only a few basic rules for application and appropriate wound design, so any surgeon should be able to switch from stitches to glue with minimal trial and error.

Some surgeons may feel more comfortable using sutures for certain parts of drainage implant surgery—e.g., attachment of the plate to sclera—while readily adopting glue for other parts of the procedure. (This may be especially true while they're transitioning to the use of glue.) A "hybrid approach" combining glue and sutures is certainly acceptable.

My Technique

About seven years ago I began converting my Ahmed valve surgeries, and to some extent my Baerveldt surgeries, into sutureless surgeries. (The reason I use this approach more with my Ahmed valve surgeries is that implanting a Baerveldt shunt—as well as the new Ahmed ClearPath device—requires a 7-0 vicryl suture to ligate the tube, so you're already using one stitch.)

In traditional tube shunt surgery we place a significant number of sutures—usually two stitches to hold the plate to the sclera; two more stitches to hold the tube to the sclera; in many cases four stitches to anchor a patch graft around the tube entry site; and then several more stitches to close the conjunctiva. This is time-consuming, and as noted, the material used for stitching is a foreign body; that creates additional inflammation beyond what's caused by the surgery itself.

In my sutureless surgery I primarily use two types of glue, which work similarly: Tisseel fibrin glue (Baxter Healthcare) and ReSure ocular sealant (Ocular Therapeutix), a polyethylene glycol hydrogel. Using either one involves mixing two solutions that

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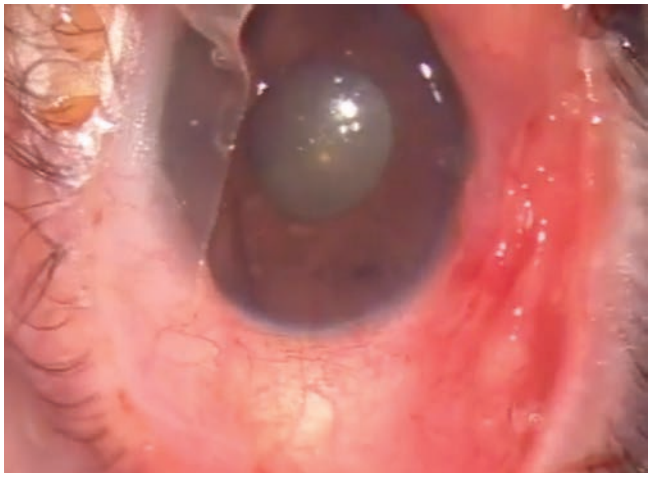

The stitchless Ahmed valve implantation is complete.

interact to form the glue. This is generally done right on the tissue that needs to be glued, and right at the time of application to the tissue. In my experience, both products work equally well; cost concerns and/or surgeon preference may influence which one is used in a given practice or situation.

Part of a successful sutureless surgery involves using a different wound construction to allow the ocular tissue to retain these implants. When implanting the Ahmed shunt I first make a conjunctival peritomy about 5 mm posterior to the limbus. That positioning allows tension-free wound closure. (Glue may fail to hold the tissues together if they're under significant tension that's trying to pull them apart.)

Second, I place the valve very posteriorly; then I gently tug on the tube to make sure that the plate is sitting comfortably behind the equator.

Third, I get the tube to stay put against the sclera by making a long, 4- to 5-mm scleral tunnel using the 23-ga. needle. This holds the tube in place, keeping the tube tip from sliding or moving.

Fourth, I lay a patch graft over the tube, where it will be glued in place. I position it so it sits below the conjunctival incision, which will help with closure. I then glue all of that together in one pass. The glue dissolves without incident over the first postoperative week.

You can see me using this technique on YouTube at youtube.com/watch?v=rTr5QhBZMMc.

Glues do a nice job of holding tissues together, but they can't withstand a tremendous amount of pulling on the tissue. If you still end up with tension on the wound, you may need to add a stitch.

Strategies for Success

To help prevent any missteps when adopting this approach to tube shunt implantation, keep these strategies in mind:

• ***Glues work best on dry tissue.*** Glue will fail if the tissue is very wet. So, if you have a patient who is bleeding a lot, or a surgical wound that's leaking aqueous, you'll need to temporarily stop the flow of aqueous or blood. If you can dry the tissue and apply the glue in a controlled setting, it should work well.

• ***Avoid wound construction that will leave the wound under a lot of tension.*** As noted, glues do a nice job of holding tissues together, but they can't withstand a tremendous amount of pulling on the tissue. To reduce tension on the wound, I don't make the incision at the limbus. Instead, I make the incision about 5 mm posterior to the limbus, where my patch graft will be placed. If you still end up with tension on the wound, you may need to add a stitch.

• ***If you have concerns, err on the conservative side and add a stitch.*** Generally, it's OK to be cautious and suture if you have any doubts about the security of the glued tissues (well-founded or otherwise). If you apply too much glue, you can trim the glue with a Westcott scissor.

• ***Eye rubbing may not be a contraindication.*** If the patient is a known eye-rubber, you might think it would be a bad idea to use glue. However, I'm not sure that's true, because patients tend to rub the eye more when there's a stitch, thanks to the foreign body sensation. Performing the surgery in a way that reduces the foreign body sensation may actually cause less postoperative eye rubbing. Use your judgment, and try to understand why the patient is rubbing the eye.

Taking advantage of the benefits of working with glue, I've personally done more than 1,000 sutureless Ahmed valves, and I continue to do them to this day. REVIEW

Dr. Radcliffe is a clinical associate professor at NY Eye and Ear Infirmary, and practices at the New York Eye Surgery Center. He is a consultant to Ocular Therapeutix and New World Medical.

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Advances In Intraoperative OCT

These new additions to the OCT arena may help with surgical maneuvers, but new research could improve them further.

Duriye Damla Sevgi, MD, and Justis P. Ehlers, MD, Cleveland

Over the past decade, there have been major advances in the field of intraoperative optical coherence tomography. From the development of the portable OCT probe to the first microscope-integrated system, intraoperative OCT has evolved from a research idea to a clinically viable technology. Advances such as heads-up visualization and microscope-integration, as well as the results from large clinical studies, have pushed the field forward.

While the feasibility and potential utility of intraoperative optical coherence tomography has been demonstrated both in clinical studies and in real-world usage, several areas of enhancement are needed to enable iOCT to be part of a seamless surgical feedback platform. Image quality, improved efficiency, OCT-compatible surgical instrumentation, automated analysis software, instrument tracking systems and enhanced visualization systems are all areas of focus for improvement for the future. This update will focus on iOCT's development, especially over the past five years, and potential future directions for technical advances.

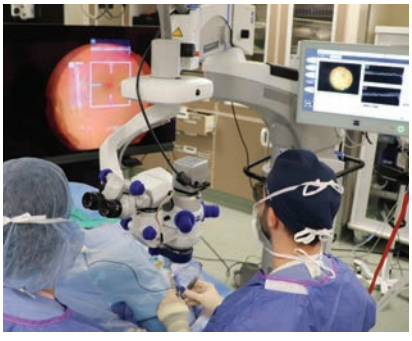

Figure 1. Digitally-enabled 3D iOCT.

The Latest Advances

Intraoperative OCT systems have advanced in several ways in recent years in an effort to make them more useful to surgeons.

• ***OCT-compatible surgical instruments.*** Current metallic surgical instruments limit visualization of the iOCT during real-time maneuvers, particularly in posterior segment surgeries. Light scattering and shadowing from metallic instruments limit visualization of the tissue-instrument interaction.[1,2,3] Studies have demonstrated that static imaging (i.e., stop and scan) is preferred in most posterior segment cases, which may be related to the lack of OCT-friendly instrumentation.[4] Semi-transparent materials with diffuse light-scattering profiles yield better compatibility with OCT, resulting in greater visibility of the instrument tip and less shadowing of the underlying tissue.[3]

Surgical tools with OCT-compatible tips are currently under development. *Ex vivo* experience with these instruments has demonstrated excellent visualization of the instrument tip edges and angles in cadaver eyes. Shadowing was minimal to none with membrane scrapers and a surgical pick. With vitreoretinal forceps, a slight increase in shadowing was noted, due to the instrument's more complex design.[5]

Further research into instrument reliability and subsequent advances in OCT-compatible surgical instruments are needed to maximize the usefulness of real-time iOCT. Beyond material changes, image processing solutions, such as spatial compounding, have been explored to minimize underlying shadowing while maximizing instrument visualization.[2]

• ***Instrument tracking systems.*** Precise instrument tracking may be

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essential for the seamless integration of real-time iOCT into the operating room, and to maximize its clinical utility. Acquisition of optimal OCT images likely requires a high sampling density and fast frame rate, which result in a limited field of view. In current systems, it's challenging to maintain the iOCT centration at the point of interest while performing surgical maneuvers. Opportunities for tracking include using the microscopic video feed for identification of the instrument's tip by machine-learning algorithms.[6] Another option is to track the instrument handles using stereo cameras. The 3D position of the instrument tip is then computed based on the instrument geometry.[7] Research is needed to evaluate these various approaches to tracking.

• ***Intraoperative Volumetric OCT.*** In current commercial iOCT systems, real-time OCT visualization is currently limited to B-scans of variable orientation. Volumetric visualization provides a unique opportunity for real-time iOCT. Current spectral domain systems are unable to create live volumetric imaging due to low scan speeds, computational challenges with volume rendering and the high requirements of postprocessing. The significantly increased imaging speed associated with new graphics-processing technologies and new swept-source OCTs has enabled real-time volumetric visualization.[8]

• ***Visualization of the OCT data stream.*** One of the most important advances that came with microscope-integrated iOCT systems was giving the surgeon the ability to have concurrent visualization of the OCT data stream and the surgical field by injecting the OCT data stream into the microscope ocular.[3] More recently, advances in 3D display technologies and 4K high-definition visualization have enabled surgical procedures to be performed using these digital systems.[4,9] The feasibility of using iOCT visualization in conjunction with 3D digital systems has also been demonstrated.[10] In these systems, the OCT B-scans are displayed on the large-screen monitor simultaneously with the image of the surgical field. Emerging visualization technologies, such as immersive visors, provide additional opportunities for integration.

• ***Additional areas of development.*** Other areas of interest for emerging improvements are automated segmentation software, virtual reality visualization and robot assisted, iOCT-guided surgeries.[6] Further research is needed, however, to improve these technologies to a level of reliability that's sufficient for the OR.

The Evolution of iOCT

Here's a brief look at how we arrived at the iOCT machines we have today.

A major shift that initiated the evolution of OCT into the operating room was the development of a handheld OCT. The first design of portable OCT was reported in 2001.[1] Bioptigen developed the first commercial handheld ophthalmic OCT probe in 2007; it was most frequently used for pediatric imaging during exams under anesthesia. In 2009, handheld OCT was first described during incisional surgery.[2] Handheld OCT systems provided excellent image quality, but also presented specific imaging challenges, including pauses in surgery, limited aiming stability and challenging reproducibility. To make image acquisition easier and improve the imaging workflow, mounting systems were developed to tether the portable probe to the microscope head. Microscope-mounted OCT systems allowed for foot-pedal X-Y-Z control that enabled excellent image reproducibility and decreased image acquisition times.[3]

Broader use of iOCT followed the introduction of commercial microscope-integrated OCT systems that provided a more seamless platform for imaging during surgery. Folding the OCT scanning beam into the microscope optics provided the first opportunity for true "real-time" OCT and parfocality with surgical field visualization. The first generation of microscope-integrated iOCTs demonstrated the potential to visualize real-time instrument interactions with tissue.[4-6] Second-generation microscope-integrated iOCT systems provided electrical focus and heads-up display.[7-9] More recently, high-speed, swept-source iOCT systems have allowed for real-time volumetric OCT visualization.[10] Alternatives to microscope integration have also been explored, including the integration of OCT into intraocular fiber probes with potential advantages in cases in which significant opacities limit conventional iOCT imaging.[11,12]

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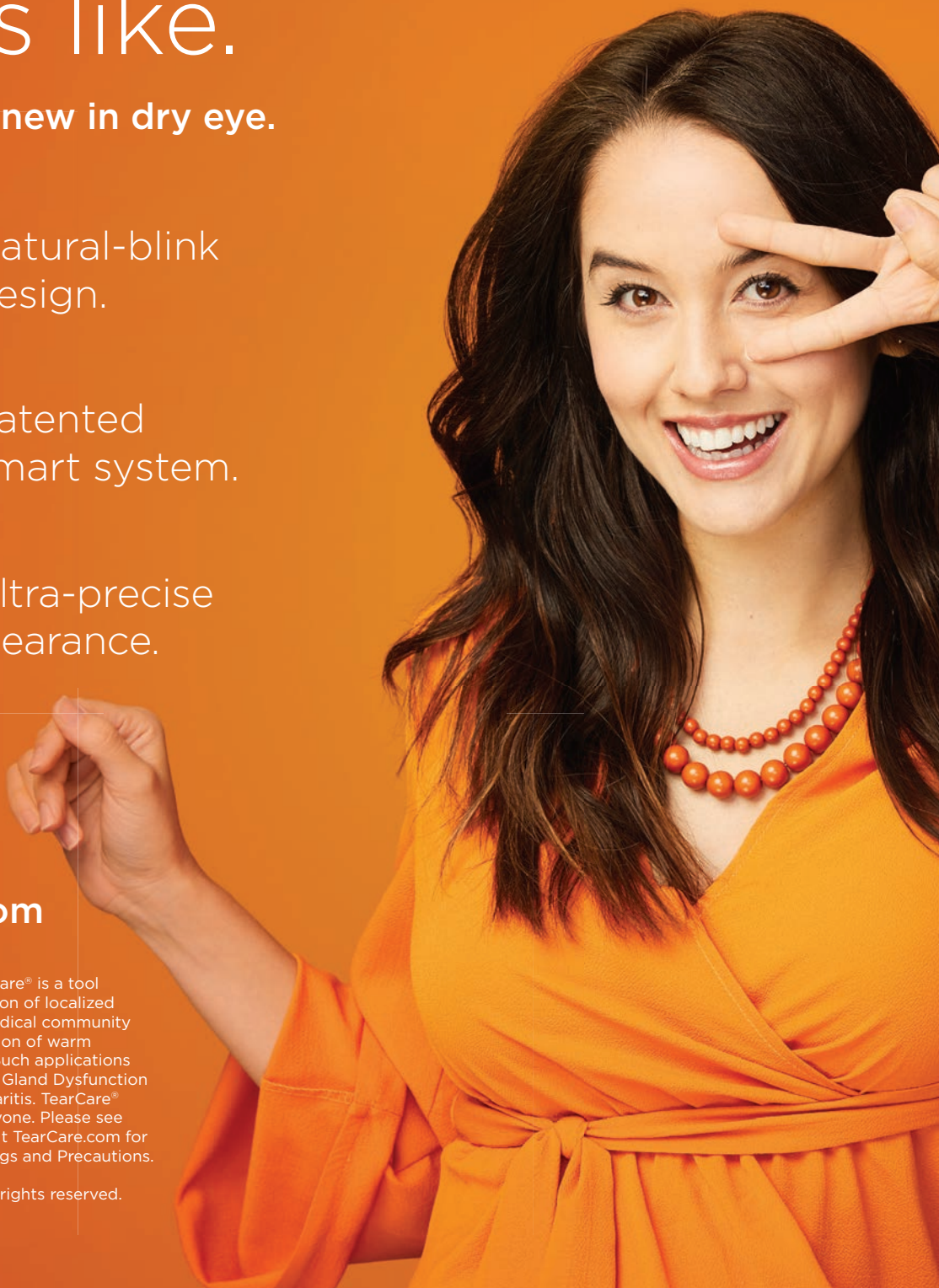

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bers of the American Society of Retina Specialists (presented at the recent ASRS meeting in Chicago) found that only a quarter of the respondents have used iOCT, the potential benefits of iOCT have been demonstrated in various anterior and posterior segment procedures, including lamellar keratoplasty, cataract surgery, glaucoma procedures, membrane peeling procedures and retinal detachment repair.[4,11,12-16]

The number of studies investigating the clinical impact of iOCT is increasing each year. PIONEER was the first large scale (n=531) prospective clinical study that examined the potential benefits of iOCT with a microscope-mounted portable OCT setup. This study demonstrated that iOCT informed surgical decision-making in a significant number of anterior and posterior segment procedures.[11] DISCOVER, the largest prospective study to date (n=837 at year three, now more than 2,000 subjects), demonstrated that microscope-integrated OCT provided intraoperative information that impacted surgical decision-making in 43 percent and 29 percent of anterior and posterior segment cases, respectively.[4] Additional studies have demonstrated similar results regarding the impact and value of iOCT for a given surgical procedure, as well as providing evaluations of system ergonomics and iOCT functionality.[4,9,10,14,16]

• ***Anterior segment surgery.*** One of the most frequently reported applications for iOCT in the anterior segment is lamellar keratoplasty procedures, in particular Descemet's stripping automated endothelial keratoplasty and Descemet's membrane endothelial keratoplasty. Multiple studies have described the potentially important role for iOCT in evaluating graft apposition and subclinical interface fluid in DSAEK procedures.[10, 14,15,18] Also, DMEK has been shown to potentially benefit from iOCT when it's used to identify graft orientation and apposition and to limit the need for the S-stamp technique.[19,22]

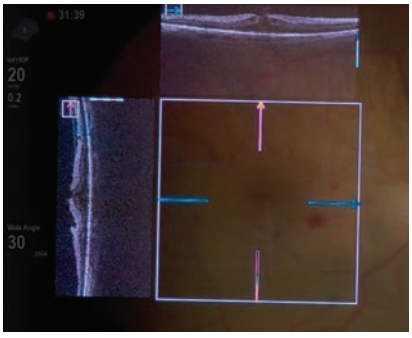

Figure 2. Post-peel iOCT following epiretinal membrane removal, confirming removal of the underlying membrane.

In cataract surgery, iOCT may be helpful for evaluating corneal incision morphology, posterior capsule status and postoperative intraocular lens position. One study found that iOCT yielded anterior chamber depth measurements, posterior capsule assessments and IOL calculations that were more accurate than preoperative biometry measurements.[16] Data related to iOCT utility in glaucoma procedures is more limited compared to other anterior segment procedures. In addition to aiding visualization of the ocular anatomy and confirming surgical goals, potential applications of iOCT in glaucoma surgery include determination of scleral graft depth, detecting any plugging of the iris and helping with proper tube placement.[13]

• ***Posterior segment surgery.*** In posterior segment surgeries, iOCT provides immediate feedback that can influence surgical maneuvers and management plans or confirm surgical endpoints. Studies have suggested that iOCT may add valuable information in more than half of cases and may alter surgical decision-making in nearly 30 percent of them.[4]

The potential clinical utility of iOCT appears to be particularly high in membrane-peeling cases.[11,17,20] In these cases, iOCT can provide crucial information about the presence of residual membrane. DISCOVER showed disagreement between iOCT findings and surgeon impressions on the completeness of membrane peel in 26.8 percent of the patients. iOCT findings both prevented unnecessary maneuvers by confirming the surgical goal had been reached in some cases and identified the need for additional peeling to remove residual membranes in others.[4]

Beyond membrane peeling, studies have shown a potential role for iOCT in other procedures, including retinal detachments, proliferative diabetic retinopathy and vitreous hemorrhage.[4,14,21] In addition, more complex procedures have been described using iOCT feedback and may benefit from intraoperative imaging, such as retinal prosthesis placement, retinal biopsy and delivery of targeted therapeutics (e.g., gene therapy, stem cell therapy and pharmacotherapy).[4,23-25] In these cases, iOCT may provide information about tissue configurations, visualize the tissue/implant interface and confirm the location and volume of therapeutic delivery.[4,23-25]

In conclusion, integration of OCT into the operating room is a potential paradigm shift in surgical visualization during ophthalmic surgery. Rapid advances in technology in recent years have allowed for the introduction of commercial iOCT systems. Significant advances are still needed in order for iOCT to reach its full potential, however, and only a small percentage of surgeons have used it. Upcoming technologies may expand the usefulness of iOCT in a wider variety of conventional and emerging interventions. REVIEW

Dr. Sevgi is a research fellow at the Cleveland Clinic. Dr. Ehlers is The Norman C. and Donna L. Harbert Endowed Chair for Ophthalmic Research and director of The Tony and Leona Campane Center for Excellence in Image-Guided Surgery and

Advanced Imaging Research at the Cleveland Clinic's Cole Eye Institute.

Dr. Sevgi has no financial interests.

Dr. Ehlers' disclosures are as follows:

Consultant to Leica, Zeiss, Alcon, Thrombogenics, Regeneron, Genentech, Allegro, Allergan, Roche and Novartis.

Research and Equipment Support: Alcon, Regeneron, Novartis, Genentech, Thrombogenics and Boehringer-Ingelheim.

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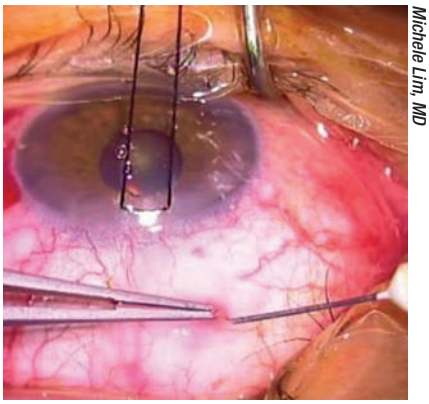
tients with disc photos (not OCT)," he recalls. "We had timolol for primary medical therapy along with drugs such as pilocarpine, epinephrine and dipivefrin (Propine). We treated patients with trabeculectomy, had started using antifibrosis drugs (5-fluorouracil), and were gaining experience with glaucoma drainage implants. Use of drainage implants was accompanied by serious complications, and we continued to perform an occasional full-thickness filter in order to achieve low postop IOP."

Dr. Netland says the subspecialty has come a long way since then. In terms of monitoring the disease, OCT has become useful for glaucoma specialists. In fact, physicians are pushing it further than was once thought possible. "Once you broaden your scanning to include the macular region," wrote Senior Editor Christopher Kent in our August issue's Technology Update, "OCT may be very useful, even in advanced disease."

Another major change in the treatment of glaucoma came with the approval of Xalatan (latanoprost; launched by Pharmacia & Upjohn) in 1996, followed by subsequent approvals of other prostaglandin analogs, and their promise of q.d. dosing. In a piece in the July 1996 edition of *Review*, glaucoma specialists Eve Higginbotham, Carl Camras, Dale Heuer, Alan Robin and Thom Zimmerman expressed their excitement over Xalatan. "For the first time in two decades, ophthalmologists have what we believe to be a truly new 'first-line' glaucoma drug …" they wrote. "Because our experience with this drug was so positive during the investigation, we believe clinicians may consider latanoprost as a first-line therapy for glaucoma, particularly for patients who have a cardiopulmonary contraindication to beta-blockers, as well as normal-pressure glaucoma patients."

Dr. Netland notes that, fortunately, there is now an array of new medications, including generic latanoprost, Vyzulta (latanoprostene bunod, Bausch + Lomb), Rhopressa (netarsudil, Aerie), Rocklatan (netarsudil + latanoprost, Aerie) and Xelpros (latanoprost without BAK preservative, Sun Pharma).



Michele Lim, MD

The advent of the use of mitomycin-C, shown here being injected, helped change the course of many filtering procedures.

Looking back over the past quarter-century, Dr. Netland closes with some very kind words. "*Review of Ophthalmology* has informed and updated us, provided important new information and given perspectives that have strengthened our clinical practice and helped 'move the needle" forward,' " he says. "I have personally enjoyed working with the outstanding professionals at *Review* for all of its history. Congratulations on reaching a milestone anniversary, and sincere best wishes for the future." REVIEW

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Seems Like Yesterday …

It's been quite a while since I've shared my thoughts on these pages. My column, appearing dependably on the last page of every issue between 1994 and 2001, was a window into the world of one comprehensive ophthalmologist trying every day to make a difference and keep his sanity. I can't say that over the past 25 years it's gotten any easier. Well, let's be frank, it's gotten a lot harder. Keeping up with the virtual torrent of new information, technology and treatment modalities is challenging enough and seems to have accelerated mercilessly. Dealing with the changes in delivering that care—running a practice, working for or with an institution, or even a vulture (er, *venture*) capitalist—has made simply providing that care the easy part for many of us.

The past quarter-century has seen not only the greatest advancemes in eye care, it's seen the greatest changes in health-care delivery. And for all that change, I for one have grave concerns that the current system of providing that care is on the precipice of collapse. Paying for all these wonders of the 21st century is beyond challenging. Medicare is facing a fiscal cliff within the next five years, commercial insurance is again becoming unaffordable and the number of those without insurance is on the rise—this despite new reimbursement cuts and new limits on our practices. However, in looking back at the past 25 years, one thing I can say is that while at many times it seemed there was no way forward, we found a way. Together, as a community of dedicated physicians, amateur businesspeople and decent human beings, we managed to survive, innovate, educate, persist and even thrive. I have great hope that we can continue to surprise even ourselves with our success.

Review of Ophthalmology was founded 25 years ago on the premise that with so much information and so much change, there needed to be a place to distill and share all this in a format that was approachable, efficient and useful. As a founding editor, I hope that we have succeeded. Congratulations *Review*, and here's to the next 25!

—Mark H. Blecher, MD
Chief Medical Editor

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(Continued from page 57)

intraoperatively manage a retinal tear caused by a pars plana vitrectomy. Retina surgeons, on the other hand, routinely check the pars plana by scleral depression after they complete a vitrectomy. They can treat any retinal tears they find—right then and there. Anterior segment surgeons almost universally do not or cannot do this. And that means when anterior segment surgeons perform a pars plana vitrectomy, they take on higher risks and put their patients at higher risks than retina surgeons do.

Trocar systems, an important advance, lower the risk of traction on the vitreous base, but they're risky in an open eye because the globe can collapse from the pressure of insertion. This point is important to consider because we anterior segment surgeons usually don't know that we need a vitrectomy until the eye is already open. Retinal surgeons routinely remove all the vitreous in the eye before operating on the retina. They also perform pars plana surgery quite regularly, while we do it very rarely. Sub-specialists like Steve Charles are really good at it. To be candid, we anterior surgeons, for the most part, are not very good at it.

In Closing

At the completion of the anterior vitrectomy, use triamcinolone acetate to confirm the anterior chamber is free of vitreous. You'll find limbal vitrectomy is a very effective way to remove vitreous from the posterior chamber without bringing vitreous forward—as long as you perform bimanual vitrectomy with watertight incisions and place the cutting port well behind the posterior capsule.

Dr. Maloney is director of the Maloney Vision Institute in Los Angeles and clinicial professor of ophthalmology at the David Geffen School of Medicine at UCLA. He reports no financial interest in any products mentioned.

(Continued from page 59)

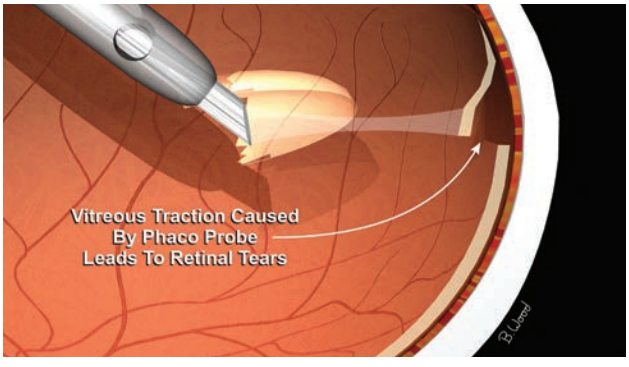

Figure 3. The phaco tip aspirates vitreous collagen fibers, causing acute vitreoretinal traction and leading to a retinal tear and detachment.

trocar cannula. Remember that a trocar-cannula system requires greater insertion force, produces much higher intraocular pressure during insertion, and is therefore more likely to cause wound disruption and iris prolapse and even penetration of the opposite side of the eye. The primary purpose of cannula-based surgery is to protect the wound during multiple tool exchanges, which is not relevant to anterior vitrectomy during cataract surgery.

To prevent wound disruption when performing any anterior vitrectomy, the anterior segment surgeon must make sure the cataract wound is sutured, not hydrated, and this is true whether or not the surgeon is using a trocar-cannula system. In addition, to avoid complications often cited by advocates of limbal-based anterior vitrectomy, the pars plana surgeon needs to keep in mind that a scleral tunnel approach to pars plana wound construction is inappropriate for anterior vitrectomy during cataract surgery. This is because a relatively soft eye can lead to instrument insertion under the retina or in the choroid, resulting in catastrophic suprachoroidal hemorrhage and/or retinal detachment. A straight-in approach, with the cutter roughly perpendicular to the scleral surface and without a scleral tunnel, is the safest technique.

Parting Thoughts

In general, keep this point is mind: There is no such thing as a "simple" anterior vitrectomy. Patients don't want—nor do they expect—a retinal detachment after cataract surgery. It's critical, of course, for us to do everything we can to prevent such a poor outcome, employing vitrectomy as safely and effectively as possible.

When the need for vitrectomy arises during cataract surgery, as it will from time to time, surgeons need to be prepared to act quickly and confidently. The pars plana approach will help them succeed if they apply these principles. REVIEW

Dr. Charles is a clinical professor of ophthalmology at the University of Tennessee Hamilton Eye Institute. Contact him at: Charles Retina Institue, 6401 Poplar Ave., Ste 190, Memphis, Tenn. 38119. scharles@att.net.

He consults with Alcon.

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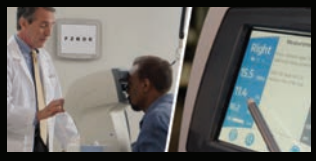

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A ClearPath to Lower Intraocular Pressure

New World Medical has announced the availability of a new option for glaucoma surgeons performing tube shunt surgery as a means to lower intraocular pressure: the Ahmed ClearPath Drainage Device. The valveless ClearPath has a flexible plate contoured to conform to the curvature of the eye. Its suture points are positioned more anteriorly than those of other valveless drainage devices to make them easier to visualize and access during surgery, the company says.

The ClearPath is available in two sizes, 350 mm^2 and 250 mm^2. The model 350 plate surface is positioned more posteriorly to avoid muscle attachment points, and the 250 mm^2 is designed to be a true single-quadrant implant that fits between the muscles. Both models come with an optional pre-threaded ripcord and a 23-ga. needle.

For more information, visit newworldmedical.com.

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A New OCT Option

Canon USA's Xephilio OCT-A1 optical coherence tomographer recently received U.S. Food and Drug Administration approval.

The system consists of the OCT device, the required RX Capture software, a computer and an LCD monitor The company says the new system is designed to easily image and measure the retina, retinal nerve fiber layer and optic disc. The Xephilio has a scan speed of 70,000 A-scans/second, with a resolution of about 3 µm.

The system uses real-time retinal tracking technology and automatically retains the scan position and protocol for each patient from one exam to the next, eliminating the need for manual adjustment. A mouse-controlled operation is used to engage the automated alignment, tracking, and acquisition of images. The positioning of the components of the Xephilio System allows for the operator and patient to sit side-by-side.

For more information, call (800) 970-7227, or visit usa.canon.com/eye-care. REVIEW


A new optical coherence tomographer from Canon retains the scan position from one exam to the next, aiding reproducibility.

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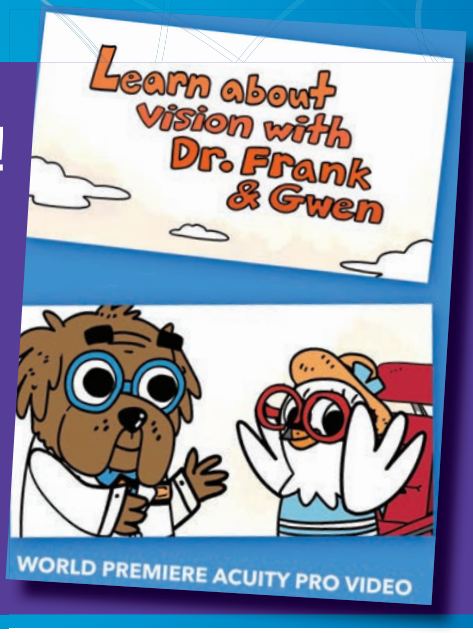

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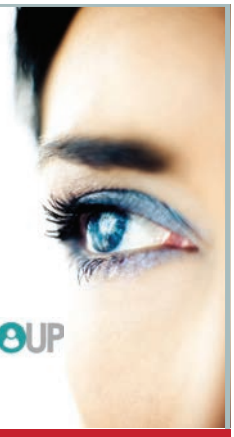

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Improving Second-eye Refractive Outcomes

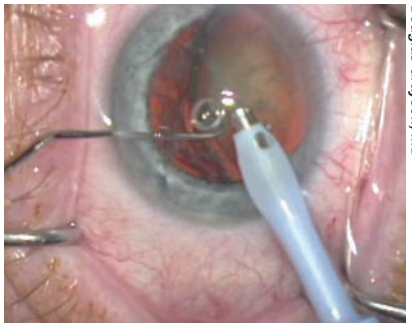
Researchers in England and Australia compared formula-specific and patient-specific methods of second-eye refinement in cataract surgery in two heterogenous datasets in order to produce more precise adjustment coefficients for improved refractive precision. Second-eye refinement is an attempt to account for inaccuracies in effective lens positioning prediction and other sources of error.

The retrospective study included 139 patients in Australia who underwent delayed sequential bilateral cataract surgery. The researchers derived adjustment coefficients for the Barrett Universal II, Hoffer Q, Holladay I and SRK/T formulas and applied them to the second eye's IOL calculation. Patient-specific optimized IOL constants were also derived from the first-eye prediction error and applied to the second-eye calculations. To test the validity of the results, the same adjustments were applied to a 605-patient U.K. dataset.

Here are the Australian-derived adjustment coefficients based on prediction error:

- Barrett Universal II: 0.30
- Hoffer Q: 0.56
- Holladay I: 0.53
- SRK/T: 0.48
- Range: 0.30 to 0.56

When applied to the dataset from the United Kingdom, 68 to 72 percent of patients were within 0.5 D of the predicted postoperative refraction (PPOR).



Douglas Grayson, MD

Researchers have found that your phaco frequency has a significant impact on effective phaco time and fluid usage. (This image depicts a different handpiece than the specific one used in the study.)

The researchers found that second-eye refinement using either method improves the refractive target in the second eye with a statistically significant positive impact on mean absolute error. They recommend using formula-specific adjustment coefficients only if the first-eye prediction error is greater than 0.5 D and if interocular symmetry is present. They developed the following formula: Adjustment =

PPOR + (formula-specific adjustment coefficient *x* first-eye PE).

J Cataract Refract Surg 2019;45:1239-1245.

Turnbull A and Barrett G.

Safer Phaco Frequencies?

In a randomized, controlled trial in New Delhi, India, researchers grouped 160 eyes of 160 patients with grade 4.0 to 6.9 senile cataract into two groups, one receiving lower-frequency (28 kHz) phacoemulsification (Group A, n=80) and one receiving higher-frequency (42 kHz) phacoemulsification (Group B, n=80). A Megatron S3 phacoemulsification machine was used. Its handpiece functions were between 27 and 55 kHz. Effective phaco time and estimated fluid usage were compared intraoperatively, and endothelial parameters were assessed over one year.

The researchers found that the cataract cases performed in Group B had significant reductions in effective phacoemulsification time and estimated fluid usage compared to Group A. Over one year of follow-up, Group B also had significantly higher endothelial cell density. This difference in cell loss after one year was found to be statistically significant, and the researchers concluded that higher frequency ultrasound is more effective and safer than lower frequency for moderate to hard cataracts.

The researchers suggest that the more localized action of higher frequency phacoemulsification may help spare endothelial cells during cataract surgery. REVIEW

J Cataract Refract Surg 2019;45:1285-1293.

Dewan T, Malik PK, Kumari R.

A young man presents at the Wills Eye Oculoplastics Department with eye pain, pressure and limited motility.

Cherie A. Fathy, MD, Mary Stefanyszyn, MD

Presentation

A 23-year-old male presented to the Wills Eye Hospital Oculoplastics clinic with a chief complaint of eye pain and pressure, as well as limitation in upgaze. The patient was referred from an outside provider for a second opinion regarding potential treatment and management.

Medical History

The patient's medical history was notable for daily headaches, depression, hypertension and sciatica. He had jaw surgery to correct midface hypoplasia. Medications included amlodipine, escitalopram, dronabinol and a myriad of homeopathic therapies. He was a former smoker who had quit two months prior to presentation. His family history was significant for Graves' disease.

Examination

Ocular examination revealed a visual acuity of 20/20 in the right eye and 20/30 in the left. Pupils and confrontation visual fields were normal in both eyes. Intraocular pressures were 33 mmHg and 28 mmHg, in the right and left eyes respectively. Extraocular motility was notable for a significant limitation in upgaze *(Figure 1)*. Ishihara color plates were full in both eyes. There was no proptosis as measured by Hertel exophthalmometry, and there was no resistance to retropulsion. Anterior segment examination revealed mild chemosis in both eyes but was otherwise unremarkable. Dilated fundus examination was normal in both eyes.

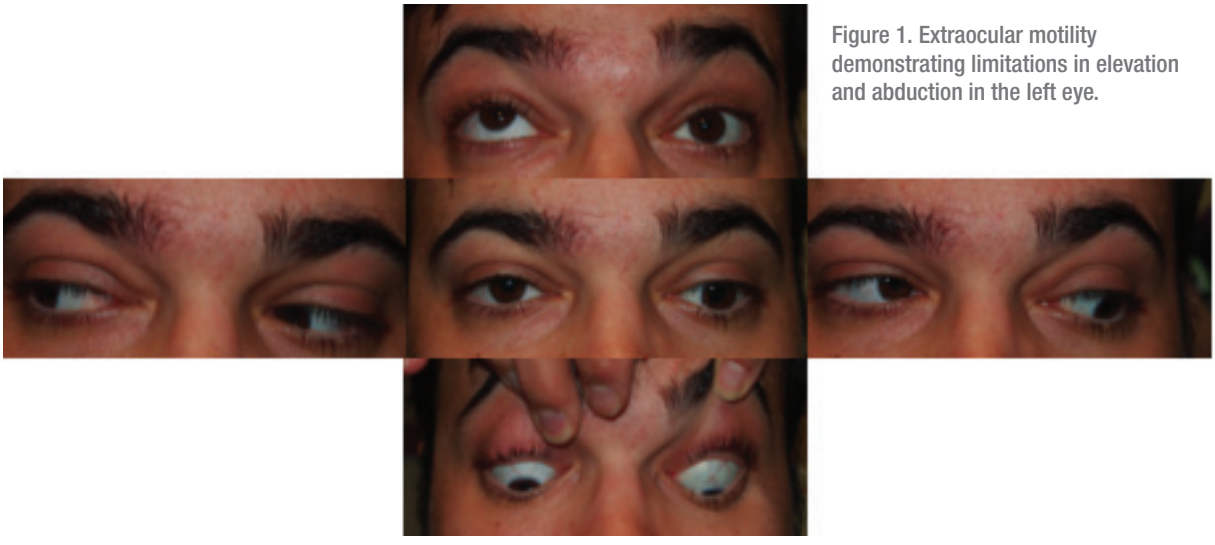


Figure 1. Extraocular motility demonstrating limitations in elevation and abduction in the left eye.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 104

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Workup, Diagnosis and Treatment

Laboratory studies, including thyroid testing, acetylcholine receptor antibodies, antineutrophil cytoplasmic antibodies and angiotensin converting enzyme returned normal. An MRI of his orbits revealed ill-defined enlargement of the left inferior rectus with surrounding fat infiltration. There was also increased enhancement of the left inferior rectus with apparent involvement of the distal myotendinous junction *(Figure 2)*. A biopsy of his inferior rectus muscle revealed dense fibrous tissue with mild chronic inflammation. There was no evidence of malignancy. This compilation of findings made orbital myositis the most likely diagnosis.

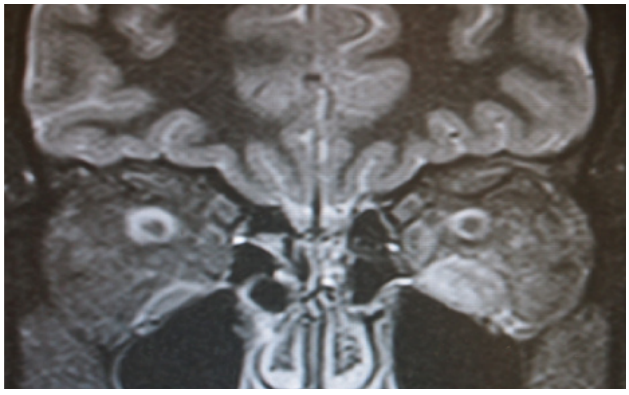


Figure 2. An MRI of the orbits revealed ill-defined enlargement of the left inferior rectus with surrounding fat infiltration. There was also increased enhancement of the left inferior rectus with apparent involvement of the distal myotendinous junction.

He was started on 60 mg of prednisone daily. He still complained of diplopia in primary gaze, which mildly improved after an intralesional injection of betamethasone/dexamethasone to the scar tissue present in the inferior fornix proximal to the left inferior rectus muscle. His headaches resolved with Botox to the brow area.

The patient was taken to surgery for exploration of his inferior fornix. During the procedure, it was noted that the left inferior rectus was firmly adhered to the orbital floor and its surrounding structures. A lysis of adhesions was performed, followed by a left inferior rectus recession with adjustable sutures. Finally, a conjunctival graft was placed to prevent re-adhesion.

After the surgery, the patient's diplopia fully resolved and he was able to taper off of all steroids *(Figure 3)*.

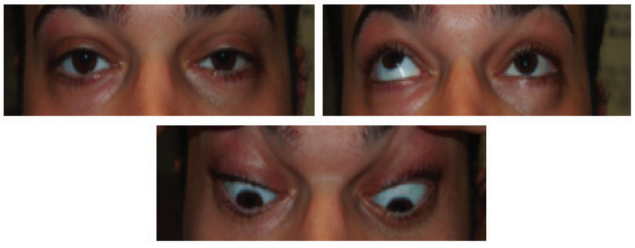


Figure 3. After surgery for lysis of adhesions and strabismus surgery, the patient had improved elevation in the left eye and resolution of his diplopia.

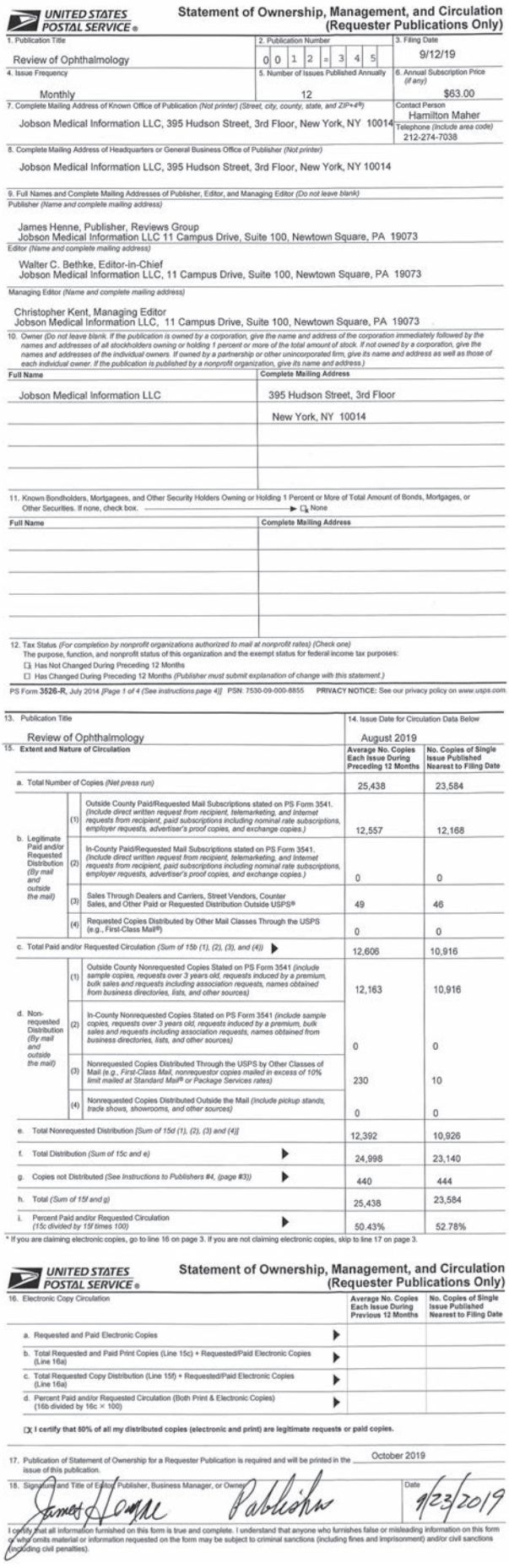
Discussion

The differential diagnosis of extraocular muscle inflammation is broad and includes inflammatory (i.e., orbital myositis, thyroid eye disease, sarcoidosis, ocular myasthenia gravis), infectious (TB, lyme, trichinosis, cysticercosis), trauma-related, and neoplastic (lymphoma, metastatic) etiologies.

The findings in our case suggested orbital myositis as the etiology. Orbital myositis is a rare inflammatory disorder of single or multiple extraocular muscles.[1] The most classic symptomatic manifestations are diplopia, unilateral presentation and orbital pain. Compared to thyroid eye disease, orbital myositis isn't commonly associated with systemic symptoms and is less likely to present with proptosis.[2]

Orbital myositis falls into a larger disease spectrum called idiopathic orbital inflammation. IOI was first described by Birch-Hirchfield in 1905 and was initially referred to as "orbital pseudotumor" because of its appearance as a benign, non-infectious, space-occupying lesion in the orbit or enlargement of an orbital structure. IOI can either be nonmyositic—such as dacryoadenitis or orbital fat inflammation—or myositic. The pathogenesis is unknown, but it has been associated with infectious processes, including upper respiratory illnesses and flulike viral illness. There may also be a link between orbital myositis and systemic immunologic disorders, such as Crohn's disease, systemic lupus erythematosus and rheumatoid arthritis.

The Orbital Society's defined criteria for the diagnosis of IOI include the presence of orbital pain, pain with eye movements and an acute or subacute onset (days or weeks) with slow progression. Imaging such as CT or MRI assist in localizing the inflammation. Atypical findings, including irregular edges, nodularity, focal intramuscular mass on imaging, orbital fat infiltration, lacrimal gland enlargement or swelling, orbital nerve enlargement and/or sinus disease may be indications for biopsy. Serologies such as inflammatory markers and autoantibodies may be falsely negative in patients with disease limited to the orbit, or with mild systemic disease. Myositic IOI can be diagnosed by clinical



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1. Publication Title	2. Publication Number	3. Filing Date
Review of Ophthalmology	0 0 1 2 - 3 4 5	9/12/19
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price (if any)**
Monthly	12	$63.00

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®): Jobson Medical Information LLC, 395 Hudson Street, 3rd Floor, New York, NY 10014 — Contact Person: Hamilton Maher; Telephone (Include area code): 212-274-7038

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): Jobson Medical Information LLC, 395 Hudson Street, 3rd Floor, New York, NY 10014

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)

Publisher (Name and complete mailing address): James Henne, Publisher, Reviews Group, Jobson Medical Information LLC 11 Campus Drive, Suite 100, Newtown Square, PA 19073

Editor (Name and complete mailing address): Walter C. Bethke, Editor-in-Chief, Jobson Medical Information LLC, 11 Campus Drive, Suite 100, Newtown Square, PA 19073

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13. Publication Title: Review of Ophthalmology — 14. Issue Date for Circulation Data Below: August 2019

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resolution or improvement in symptoms within 48 hours of starting steroids. The diagnosis may also be made with a biopsy, in which case histopathology will show a nonspecific, polymorphous infiltrate of small, well-differentiated lymphocytes (primarily T cells), plasma cells and neutrophilic and eosinophilic granulocytes. Indications for biopsy include the absence of pain, subacute onset, a loss of function resulting in extraocular motility deficits, failure to respond to corticosteroids, or a disease recurrence while tapering corticosteroids.[3]

A myriad of treatment options are available for treating IOI. If the case is mild, observation is an option. A three-week trial of nonsteroidal anti-inflammatory drugs is recommended prior to moving on to corticosteroids.[4] Corticosteroids are also considered a treatment mainstay for their immunosuppressive and anti-inflammatory effects.[5,6] The vast majority of patients respond well to steroids; however, steroid intolerance and dependence are potential side effects.[7] For those who fail steroid therapy, alternatives include radiation or immunosuppressive agents.[8] In our case, surgical resection was needed for IOI that was refractory to treatment.

In conclusion, IOI is an orbital inflammatory disease of children and adults, of unknown etiology. It occurs in the absence of known systemic disease. IOI usually responds to steroids, but it may require biopsy followed by other types of immunosuppression in refractory or recurrent cases. REVIEW

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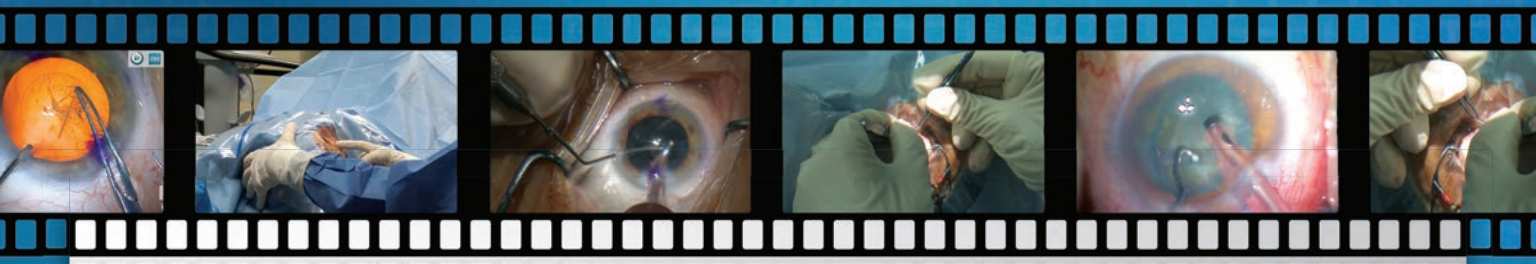

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Consult the Full Prescribing Information for complete product information.

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

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

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

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

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

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

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

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

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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Indication

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

Important Safety Information

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

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

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

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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