REVIEW® of Ophthalmology

July 2019

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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]
- Reduces the incidence of rebound iritis, postoperative pain/photophobia, and cystoid macular edema (CME) in patients without preoperative vitreomacular traction (VMT), when used with a postoperative topical NSAID (compared to postoperative topical NSAID + corticosteroid without OMIDRIA)[12]

## OMIDRIA inhibits prostaglandin release, reducing intraoperative inflammation, to prevent miosis and reduce postoperative pain[13]

**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.**

**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. Miosis prevention in femtosecond cataract surgery using a continuous infusion of phenylephrine and ketorolac. Presented at: 2018 American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. **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.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

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1% / 0.3%

REVIEW NEWS
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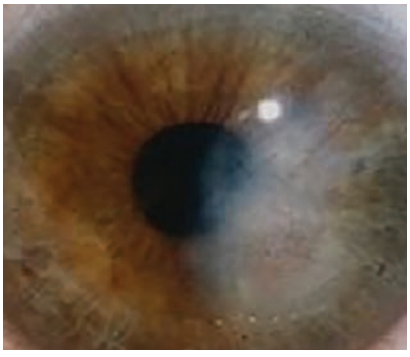
# Studies Shed Light on Postop Cataract Complications

**Two groups of international** researchers recently published studies that may help cataract surgeons minimize complications.

A group composed of researchers from the New Zealand National Eye Center at the University of Auckland and the Greenlane Clinical Centre at the Auckland District Health Board say that cataract surgeons may be able to take certain measures preop to help minimize the recurrence of herpes zoster-related ocular disease.

In what the researchers deem the largest study to date examining the outcomes of cataract surgery in eyes with a history of herpes zoster keratitis and uveitis, the researchers retrospectively studied 57 cases (57 eyes of 57 patients) in which patients with herpes zoster-related keratitis and/or uveitis had cataract surgery in the affected eye.[1] Patients were included if they had clinical presentation of HZO with keratitis or anterior uveitis, or if they had anterior uveitis consistent with a viral picture that was confirmed to be varicella zoster virus on aqueous humor tap.

The median age at the time of HZO diagnosis was 71.4 years (range: 65.9 to 76.8), and 34 patients (59.6 percent) were men. Nine patients were immunosuppressed at the time of presentation, including two with Crohn's disease, one with rheumatoid arthritis, two with chronic lymphocytic leukemia, two on low-dose prednisone for polymyalgia rheumatica and two with a solid organ transplant. No patients



were HIV-positive.

At presentation, the researchers say that 55 patients (96.5 percent) had a typical clinical presentation of HZO, with unilateral rash. Fifty-four patients were taking antivirals, and 48 of them (88.9 percent) received seven to 10 days of oral antiviral therapy. The median corrected distance visual acuity at presentation was 20/30 (range: 20/25 to 20/60). Thirty-seven patients (64.9 percent) had corneal disease at presentation, with pseudodendrites in 21 cases (36.8 percent) and disciform keratitis in 19 (33.3 percent). Forty-eight patients (84.2 percent) had anterior uveitis at presentaton.

In terms of herpes recurrence preop, 38 patients (66.7 percent) had recurrent disease, with 28 (49.1 percent) having recurrent corneal disease and 25 having recurrent uveitis. The patients had a median of two recurrences before surgery, and the median time from the last recurrence to surgery was 1.2 years (range: 0.7 to 2.4 years). Twenty-two patients (38.6 percent) had surgery less than a year after their most recent flare-up, and three (5.3 percent) had surgery fewer than three months after the last recurrence.

After the group's cataract surgeries, the HZO recurred in 23 patients (40.4 percent), with recurrences in the first two years postop being the most common. Three patients developed band keratopathy after repeated inflammation, and one had a neurotrophic keratitis with a persistent epithelial defect. There was a severe recurrence of herpes keratitis with corneal melt in the eye of a Crohn's-disease patient which ultimately required evisceration.

The study's corresponding author, Rachael L. Niederer, MB ChB, PhD, FRANZCO, of the Department of Ophthalmology at Greenlane Clinical Centre, says a couple things stood out to her from the study's findings. "Cataract surgery in subjects with previous HZO is complicated by corneal scars (43.9 percent), atrophic floppy iris (5.3 percent) and posterior synechiae (8.8 percent)," she says. "I was surprised that despite this more complex surgery, the early postoperative complications were low, with few subjects experiencing cystoid macular edema or prolonged postoperative inflammation. What really stood out from the study, was the very high rate of recurrence of zoster keratitis and/or uveitis over the first year following surgery, often with a reduction in vision to below preoperative levels." Seven patients (12.3 percent) saw a decline in their 12-month CDVA

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EDITORIAL STAFF

**Editor in Chief**
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(610) 492-1024
wbethke@jobson.com

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(212) 274-7031
ckent@jobson.com

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Reviewophthalmo@aol.com

**Business Offices**
11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039
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BPA

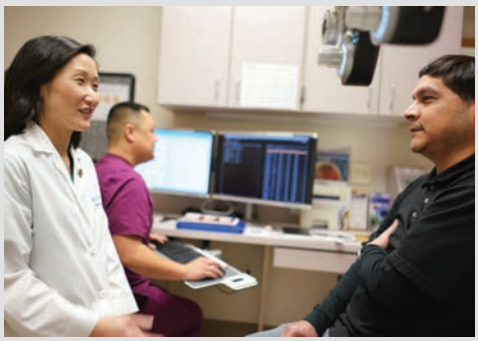
# REVIEW News

compared to their preop level. A poor visual outcome was more common in patients with a central scar, and complications during the surgery didn't correlate with decreased acuity afterward.

At this point, the researchers can't say for sure what it is about phaco that triggers a higher rate of HZO recurrence. "An increase in recurrence of herpes zoster and herpes simplex has been noticed by a few researchers following other surgery," Dr. Niederer says. "The mechanisms are unclear, but could include local trauma, release of sequestered virus, or the stress of the surgery. Herpes simplex virus has previously been isolated from the lens in a patient with previous acute retinal necrosis, so it seems plausible that sequestered virus may exist in patients with herpes zoster. We have a further study under way to examine this link in more detail. There was no difference in the rate of recurrence following complicated cataract surgery ($p$=0.727)."

Dr. Niederer says surgeons can take steps to possibly decrease the risk of a postop flare-up. "Normally in subjects with uveitis, we advocate three months of disease quiescence prior to considering cataract surgery," she says. "However, in the current study, the highest rates of recurrence of herpes zoster eye disease were seen in those with less than one year of quiescence. We therefore recommend a longer period of quiescence (ideally one year) where possible in those with herpes zoster. The role of antivirals in decreasing disease recurrence in zoster is currently unknown and we are eagerly awaiting the results of the Zoster Eye Disease Study (ZEDS) to provide more guidance on this. In our personal practice, we use three months of antiviral prophylaxis, starting on the day of surgery, for those with simple previous herpes zoster eye involvement, and one year of antiviral prophylaxis for those

## Corrections



In the May 2019 article, "EHR Systems: Room For Improvement?" the physician in this image on the left was incorrectly identified as Jennifer Lim. It is actually Davis Eye Center's Lily Koo Lin, MD. *Review* regrets the error.

In the June installment of Glaucoma Management, "Easing Your Patients' Financial Burden," the pricing data in the table on p. 62 wasn't accurate. Specifically, the per-day price shown for latanoprostene bunod was for a larger 5 ml bottle, not 2.5 ml, leading to a higher per-day price. The corrected table using a 30-day supply for the drugs appears below.

### Per-day Glaucoma Drug Price Comparison*

| BB | AA | CAI | PGA | BB+CAI | BB+AA | LBN | Netarsudil |
|---|---|---|---|---|---|---|---|
| $0.38 | $0.97 | $1.04 | $1.62 | $1.83 | $5.29 | $6.41 | $8.52 |

* Numbers from GoodRx.com, Accessed 27 June 2019.

BB=beta blocker; AA=alpha agonist; CAI=carbonic anhydrase inhibitor; PGA=prostaglandin analogue; LBN=latanoprostene bunod.

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DEXTENZA is a corticosteroid indicated for the treatment of ocular 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 (9%); intraocular pressure increased (5%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); corneal edema (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 and 76.4% in Study 2 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; 2018. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.



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with recurrent episodes of inflammation."

Researchers in New Delhi, India, say that the timing of cataract surgery appears to be a key factor for patients with chorioretinal coloboma.

In the largest case series of cataract surgery in patients with chorioretinal coloboma, the researchers reviewed the medical records of patients with chorioretinal coloboma who had cataract surgery between January 2016 and May 2018.[2] The study comprised 39 eyes of 38 patients. There were 14 women and 24 men, with a mean age of 36.74 ±15.24.

*"There was a marked difference in the baseline visual acuity of our cases compared to other studies reporting cataract surgery outcome in chorioretinal coloboma. This could have resulted in the suboptimal outcome."*
*— Praful Maharana, MD*

Preop, the mean best-corrected vision of the group was 1.83 logMAR (slightly worse than 20/800). Coloboma involving the macula was present in 46.5 percent of the cases. The cataracts were grade 2 in five cases (12.8 percent), grade 3 in seven (17.9 percent) and grade 4 in 17 cases (43.6 percent).

Other morphologies in the study included six cortical cataracts, two total cataracts, one posterior subcapsular cataract and one congenital nuclear cataract.

For the procedure itself, surgeons performed phaco in 22 eyes (56 percent), lens aspiration in five cases (12.8 percent), extracap in five cases, intracap in four eyes (10.3 percent), small-incision cataract surgery in two cases (6.7 percent) and pars plana lensectomy in one case (2.6 percent).

Immediately postop, eyes with increased intraocular pressure were managed with glaucoma drops. Eleven cases had corneal edema, which resolved with conservative therapy in nine cases; the remaining two needed endothelial keratoplasty. At one year, data was available for 13 cases (14 eyes). The mean vision at that time was 1.51 ±0.58 logMAR (slightly better than 20/800).

Looking at the study's results in relation to similar studies, the authors say that the patient age at the time of surgery likely dictates the type of surgery that's performed. In one study composed of relatively young patients (mean age: 27.7), phaco was performed in all cases. In this study and another in which patients were older (mean age: 37.6), some cases required ECCE, ICCE or lensectomy through the pars plana, which might invite complications that wouldn't be as likely to occur with phaco. The researchers also point out that the outcomes of surgery in younger patients were better; specifically the proportion of uneventful surgeries, IOL implantation rate and the rate of posterior capsule rupture were all better in the series with younger patients.

Praful Maharana, MD, one of the study's authors, says some other factors may have impacted the suboptimal outcomes. "The macular involvement rate was significantly more in our series (45.2 percent)," he notes. "In fact, there was a marked difference in the baseline visual acuity of our cases compared to other studies reporting cataract surgery outcome in chorioretinal coloboma. This could have resulted in the suboptimal outcome. The second major cause could be the associated amblyopia. "Most of the cases of CRC have had some refractive error since the early part of their lives," Dr. Maharana continues. "Due to poor access to health care or lack of knowledge on the part of the primary care physician, refractive error, especially irregular astigmatism, often goes uncorrected. This could lead to amblyopia and subsequent poor outcomes following cataract surgery."

Dr. Maharana says the main thing he learned from the study was regarding surgical timing. "One should not delay cataract surgery in patients with chorioretinal coloboma," he says. "In our area, the greatest difficulty in decision making is the unpredictable follow-up pattern of the patient after the surgery. Hence, most surgeons avoid cataract surgery while the patient has some reasonable vision. However, the result of our study suggests that the surgery should be done early.

"The standard practice of being prepared with capsular supporting devices such as CTR/Cionni, using capsulorhexis forceps for CCC, low and slow phacoemulsification, use of viscodispersive viscoelastics, and performing pupilloplasty at the end of surgery should be kept in mind. Careful follow-up is essential as the complication rate is high and the majority of patients requires laser delimitation in the postoperative period."

1. Lu L, McGhee C, Sims J, Niederer R. High rate of recurrence of herpes zoster-related ocular disease after phacoemulsification cataract surgery. J Cataract Refract Surg 2019;45:810-815.
2. Sahay P, Maharana P, Mandal S, et al. Cataract surgery outcomes in eyes with chorioretinal coloboma. J Cataract Refract Surg 2019;45:630-638.

# Keratoconus' Genetic Connection

New data adds some weight to the theory that keratoconus is driven, in part, by genetics. Researchers recently evaluated the tomographic and refractive characteristics of siblings of pediatric patients with keratoconus or the children of adults with keratoconus and found that the prevalence of keratoconus was high, warranting screening in this high-risk group.[1]

This cross-sectional study evaluated 183 pediatric first-degree relatives of patients with keratoconus and included both eyes of all participants between the ages of six and 18. The participants underwent manifest refraction, slit-lamp exams and Scheimpflug tomography—the latter of which was evaluated by two masked cornea and refractive surgeons.

The researchers found the tomography data showed 17.5 percent participants had keratoconus, while 19.1 percent were labeled as having keratoconus by objective analysis. The team found that 11.5 percent to 15.5 percent of patients with keratoconus were younger than 11, with steepest anterior curvature and thinnest pachymetry values of 44.8 ±6.5D and 515.9 ±39.2 µm. The 18 percent between the ages of 12 and 15 with keratoconus had values of 47.34 ±3.4D and 496.1 ±37.9 µm, while the 25.5 percent of keratoconus patients between 16 and 18 had 49.7 ±6.1 D and 486.0 ±66.5 µm. They add that 37.5 percent of keratoconus patients were unilateral as evaluated by tomography alone.

1. Awwad ST, Yehia M, Mehanna CJ, et al. Tomographic and refractive characteristics of pdiatric first-degree relatives of keratoconus patients. Am J Ophthalmol. June 10, 2019. [Epub ahead of print].

# AbbVie to Acquire Allergan

AbbVie and Allergan announced that the companies have entered into a definitive transaction agreement under which AbbVie will acquire Allergan in a cash and stock transaction for a transaction equity value of approximately $63 billion, based on the closing price of AbbVie's common stock of $78.45 on June 24, 2019. In the official announcement of the acquisition, AbbVie describes the deal as, a "transformational transaction for both companies" that "achieves unique and complementary strategic objectives." REVIEW

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CORPORATE PRODUCTION DIRECTOR
**JOHN ANTHONY CAGGIANO**

VICE PRESIDENT, CIRCULATION
**EMELDA BAREA**

jmi

395 Hudson Street, 3rd Floor,
New York, NY 10014

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**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).


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Based on 9669600-9669700 Revised: 02/2019


# SUBMICRON STRONG

## Engineered with SM Technology™ for efficient penetration at a low BAK level (0.003%)[1,2]

**~2× GREATER PENETRATION** to the aqueous humor[2*]

*Compared to LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%. 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, $P<0.0001$)[1,3†]
- 74% of LOTEMAX® SM patients were completely pain-free vs vehicle (49%) at Day 8 (N=371, $P<0.0001$)[1,3‡]

†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.** Cavet ME, Glogowski S, DiSalvo C, Richardson ME. Ocular pharmacokinetics of submicron loteprednol etabonate ophthalmic gel, 0.38% following topical administration in rabbits. Poster presented at 2015 ARVO Annual Meeting; May 4, 2015; Denver, Colorado. **3.** Data on file. Bausch & Lomb, Incorporated.

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**LOTEMAX® SM**
(loteprednol etabonate ophthalmic gel) 0.38%

REVIEW® of Ophthalmology

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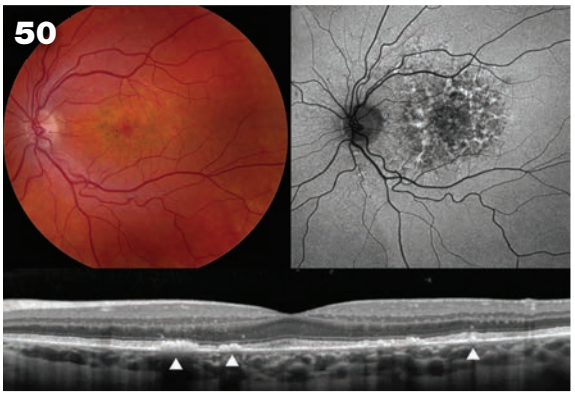
# Cover Story

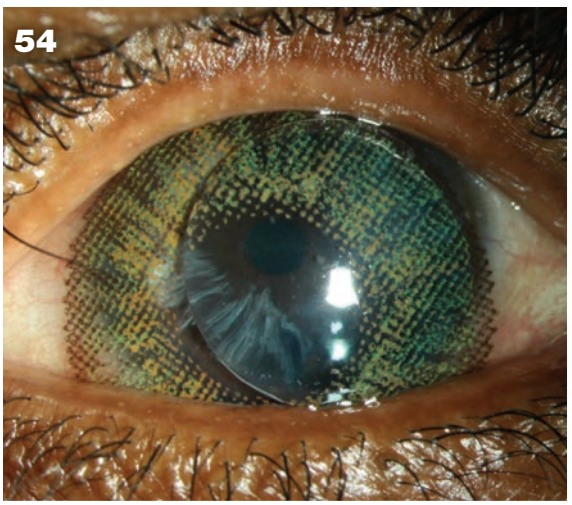


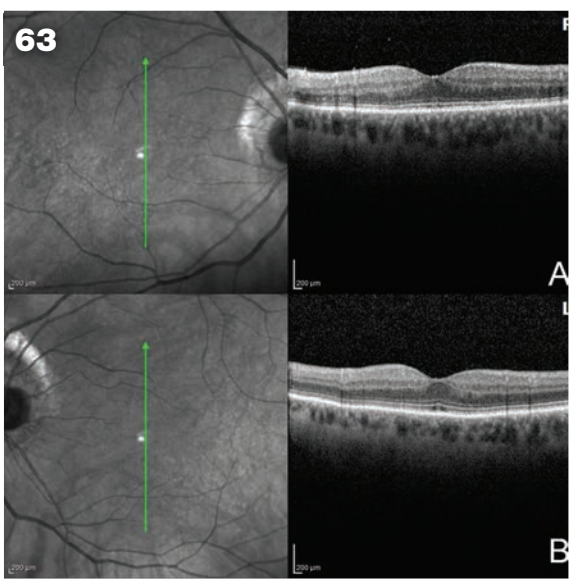
# Feature Articles

# Departments





# NEW The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation[1-3]


## With a single injection at the end of cataract surgery, anti-inflammatory efficacy begins as early as day 1 and continues through day 30[1]*

- The percentage of patients who received DEXYCU (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]

***NOW AVAILABLE***

**DEXYCU™**
(dexamethasone intraocular suspension) 9%

*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.

EyePoint™ PHARMACEUTICALS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01/2019
US-DEX-1900045

**DEXYCU (dexamethasone intraocular suspension) 9%,**
**for intraocular administration**
**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.

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

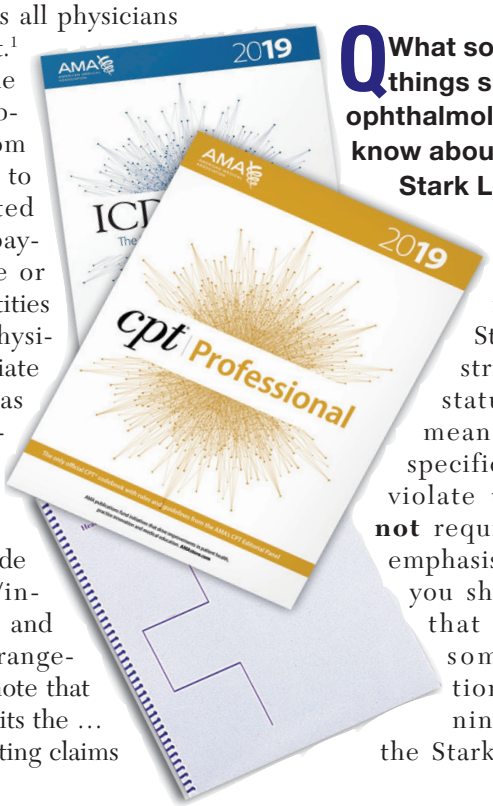
Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

# Understanding Stark And Kickback Laws

What you need to know about laws governing such things as "self-referrals" and financial arrangements between practices.

**Q I hear a lot of people talk about avoiding possible "Stark Law" violations. Why is that important?**

A The Office of the Inspector General for Health and Human Services notes that Stark is one of the top five things all physicians should know about.[1] OIG notes that the Stark Law "prohibits physicians from referring patients to receive 'designated health services' payable by Medicare or Medicaid from entities with which the physician or an immediate family member has a financial relationship, unless an exception applies. Financial relationships include both ownership/investment interests and compensation arrangements. They also note that this law "… prohibits the … entity from submitting claims to Medicare for those services … ."[2] Another name for the Stark Law is the Physician Self-Referral Law,[3] so it's useful to remember that this is about "you referring to you." It's found in section 1877 of the Social Security Act [42 U.S.C. § 1395nn].[4]




**Q What sorts of things should ophthalmologists know about the Stark Law?**

A First, CMS notes that Stark is "… a strict liability statute, which means proof of specific intent to violate the law is **not** required." (My emphasis.) Second, you should know that there are some exceptions to running afoul of the Stark Law. One of the exceptions allows "… medical practice[s] to make referrals for in-office ancillary services such as laboratory or radiology services …"[5] [these are known as designated health services]. Third, many states have their own Physician Self Referral regulations, so you should check the rules of your state. (Your state professional societies are good places to ask about this.)

**Q The previous response mentioned that "designated health services" (DHS) can be a potential Stark Law issue. What exactly are DHS and how might they affect ophthalmologists?**

A This particular issue has recently been getting a lot more enforcement attention. The main issue for ophthalmologists who are paid on a productivity-basis, by base pay and/or a bonus, is that they have to exclude certain amounts from some items done routinely in their office if that service appears on the DHS list published by CMS.[6] Most often, this is the technical component of these services, but labs are different. Lab

*This article has no commercial sponsorship.*

tests don't have a Technical Component/Modifier 26 split and the entire allowed amount is subject to Stark DHS if it appears on the list. The list of DHS services for 2019 includes the following things that are done fairly commonly in eye care (the full list is much longer):

- ultrasound tests: The A- and B-scan tests done in the office (CPT codes 76510-76519);
- OCT tests (CPT 92132, 92133, and 92134);
- tear testing (CPT codes 0330T, 83516, 83861); and
- remote imaging (CPT 92227 and 92228).

The list of codes subject to DHS regulations may change from year to year. It's usually published for the upcoming year in late November of the preceding year.

## Q What is the Anti-kickback Statute? Does it have the same concerns for me as does the Stark Law?

**A** While being in violation of either is certainly bad, the Anti-kickback Statute is much broader in scope than Stark. AKS is not about "you benefitting from referring to yourself" (that's Stark Law)—it's about "relationships between entities" in which a financial benefit that might accrue to either party might not be above board. OIG notes "The AKS is a criminal law that prohibits the knowing and willful payment of 'remuneration' to induce or reward patient referrals or the generation of business involving any item or service payable by the Federal health care programs (e.g., drugs, supplies, or health care services for Medicare or Medicaid patients). Remuneration includes anything of value … in the Federal health care programs, paying for referrals is a crime. The statute covers the payers of kickbacks—those who offer or pay remuneration—as well as the recipients of kickbacks …"[1]

AKS is not a "strict liability" standard like Stark. To be found guilty of AKS, you have to be proven to have intent (i.e., you are knowingly and willingly in violation).

*"The Government does not need to prove patient harm or financial loss to the programs to show that a physician violated the AKS. A physician can be guilty of violating the AKS even if the physician actually rendered the service and the service was medically necessary."*[1]

## Q Are there penalties under the AKS?

**A** Yes, and they can be severe. CMS notes that violators can "face penalties of up to $50,000 per kickback plus three times the amount of the remuneration." You can even run afoul of AKS and "the Government does not need to prove patient harm or financial loss to the programs to show that a physician violated the AKS. A physician can be guilty of violating the AKS even if the physician actually rendered the service and the service was medically necessary."[1]

Importantly, there are some specific, published ways that ensure that you don't violate AKS; the law refers to these as "safe harbors." OIG notes[1] that "Safe harbors protect certain payment and business practices that could otherwise implicate the AKS from criminal and civil prosecution. To be protected by a safe harbor, an arrangement must fit squarely in the safe harbor and satisfy all of its requirements. Some safe harbors address personal services and rental agreements, investments in ambulatory surgical centers, and payments to bona fide employees."[1] While some practices don't fit squarely under a safe harbor, they may not rise to the level of enforcement, or are considered low-risk.

## Q How do I find out if I have a potential issue under either Stark Law or the Anti-kickback Statute?

**A** If you are concerned in any way about specific referral, legal or financial arrangements that might violate either of these important regulations, get advice from an attorney who is well-versed in this area. It could be money well-spent. REVIEW

*Mr. Larson is a senior consultant at the Corcoran Consulting Group. Contact him at plarson@corcorancg.com.*

1. OIG. Compliance. Physician Education. A Roadmap for New Physicians. Fraud & Abuse Laws. https://oig.hhs.gov/compliance/physician-education/01laws.asp. Accessed 06/01/19.
2. OIG. Comparison of the Antikickback Statute and Stark Law. https://oig.hhs.gov/compliance/provider-compliance-training/files/StarkandAKSChartHandout508.pdf. Accessed 06/01/19.
3. CMS. Fraud and Abuse. Physician Self Referral. https://www.cms.gov/Medicare/Fraud-and-Abuse/PhysicianSelfReferral/index.html?redirect=/physicianselfreferral/. Accessed 06/01/19.
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5. Barrett & Singal. The Stark Law. https://barrettsingal.com/services/the-stark-law. Accessed 06/01/19.
6. CMS. Code List for Certain Designated Health Services (DHS). https://www.cms.gov/Medicare/Fraud-and-Abuse/PhysicianSelfReferral/List_of_Codes.html. Accessed 06/01/19.

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FLM191-1218-01


# Working with Inflow Ablative Procedures

A surgeon discusses the pros and cons of three commonly used forms of cyclophotocoagulation.

*Jeffrey Kammer, MD, Nashville, Tennessee*

**As you know,** our primary way of preventing glaucoma progression is by reducing intraocular pressure. Most procedures, including trabeculectomy, tube shunt implantation and most minimally invasive glaucoma surgeries (MIGS), reduce IOP by increasing the outflow of aqueous from the eye. The most notable exception has always been cyclophotocoagulation of the ciliary body (CPC), which alters this tissue and reduces its secretion of aqueous humor. (It may also increase outflow; more on that later.) For many years, this has been accomplished using either external lasers (transscleral cyclophotocoagulation, or TSCPC), or an endoscopic probe to target the tissue from inside the eye (endoscopic cyclophotocoagulation, or ECP). More recently, the use of a non-continuous-wave laser pattern has created a new, less-tissue-altering way to accomplish this from outside the eye (micropulse cyclophotocoagulation, or MPCPC).

All three are effective at lowering IOP, and all three have benefits and risks associated with them. Here, I'll share the pros and cons of each approach, along with pearls to help you make the most of whichever one you may be using.

## Transscleral CPC

When performing transscleral cyclophotocoagulation—lasering from outside the eye—the three risks that we're primarily concerned about are hypotony, phthisis and vision loss. These complications are rare, but they've been an issue since people started performing cyclodestructive procedures almost 100 years ago. That's because, historically, ophthalmologists have waited until patients had end-stage disease to perform cyclophotocoagulation. End-stage patients—particularly those with neovascular glaucoma—tend to do poorly regardless of how you treat them.

For example, one study of patients with advanced neovascular glaucoma compared the effectiveness of a cyclodestructive procedure and a Baerveldt tube shunt.[1] Both groups had similar rates of complications; in both groups, vision decreased by almost 40 percent despite treatment, and both groups had an 8-percent

**Eyes Receiving Primary Treatment for POAG Using Diode Laser TSCPC, Compared to the Fellow Medically Treated Eye (n=47)**

| | TSCPC-treated eye | Fellow medically treated eye | *P* value |
|---|---|---|---|
| Decrease in IOP (mmHg); mean ±SD (range) | 2.7 ±11.2 (+28 to -29) | -0.60 ±6.6 (+16 to -20) | 0.2 |
| Change in visual acuity (number [%]): | | | |
| Decrease | 9 (20) | 10 (23) | >0.25 |
| No change | 31 (70) | 30 (68) | >0.25 |
| Increase | 4 (9) | 4 (9) | >0.25 |

A study conducted in Ghana using transscleral CPC as a primary treatment for POAG found it practical and well-tolerated, with few serious complications.[4]



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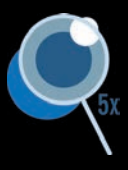


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**Analysis of Risk Factors for Hypotony after Transscleral Diode Cyclophotocoagulation**

| Factor | Odds Ratio | 95%CI | P value |
|---|---|---|---|
| Rubeotic glaucoma | 9.17 | 1.85 – 45.36 | 0.002 |
| Total energy >90 J | 0.737 | 0.181 – 2.995 | 0.668 |
| Age >50 years | 0.537 | 0.145 – 1.988 | 0.347 |
| Earlier operations | 0.295 | 0.036 – 2.431 | 0.232 |
| Repeat TCP | 1.69 | 0.319 – 8.954 | 0.534 |

In a study of 90 eyes that underwent TSCPC at the Singapore National Eye Center between 2005 and 2007, an underlying diagnosis of neovascular (rubeotic) glaucoma was found to be a significant risk factor for postoperative hypotony. Because in the past TSCPC was often reserved for advanced glaucoma cases, findings such as this may partially explain why hypotony has been thought of as a frequent side effect of TSCPC.[2]

risk of phthisis. So a tube shunt also produced less-than-ideal results in these patients.

In fact, other studies have shown that neovascular glaucoma—i.e., advanced disease—is far and away the largest risk factor for developing hypotony following CPC.[2] (*See table, above.*) As Harry Quigley, MD, noted in one of his studies involving TCP, "Although phthisis and enucleation occurred, they were uncommon and frequently associated with severe baseline status and complex additional ocular problems."[3]

The fact that this procedure is safer than its reputation suggests has been confirmed by a number of studies. In studies in which TCP is used to treat glaucoma patients at an earlier stage of disease, not only is it effective, but patients tend to do quite well. For example, in one study, TPC was compared to traditional glaucoma drops as primary treatment in fellow eyes.[4] Researchers found that in the 19 eyes that had baseline good vision, only one experienced a decrease in vision over the course of the study, and there was no significant difference in visual acuity between the fellow eyes at the final visit. (*See table, p. 18.*) Also, TCP can be effective as an adjunctive treatment in patients with glaucoma drainage implants, with a low rate of complications.[5]

The implication is clear: If you start with patients who have better prognoses, they'll do better regardless of which therapy regimen you choose, and TSCPC is an option worth considering.

## Endoscopic CPC

I think of endoscopic cyclophotocoagulation as the forgotten MIGS procedure. (I know some doctors don't consider ECP to be MIGS, but I believe it fits the description of a MIGS procedure quite well.) It doesn't get the attention that the more recent MIGS procedures get; they're new and exciting and have company reps promoting them, while ECP has been around for 10 or 12 years. Nevertheless, the clinical data show that it has efficacy and a favorable side-effect profile. In addition, it's reusable and doesn't leave any hardware inside the eye, and it can be used in a large number of patients. In particular, it can be used as an adjunctive treatment, because it combines well with other MIGS. Most MIGS increase outflow; ECP helps to decrease inflow, making them symbiotic.

One thing we have to be concerned about with ECP is IOP spikes. Two separate studies found almost the same incidence of IOP spikes associated with ECP. A 2010 study involving 368 eyes with at least two years of follow-up reported an IOP spike incidence of 14.1 percent.[6] A study conducted by the ECP Collaborative Study Group involving 5,824 eyes with a mean follow-up of 5.2 years found an IOP spike rate of 14.5 percent. The data were reported at the American Society of Cataract and Refractive Surgery Symposium on Cataract, IOL and Refractive Surgery in San Diego in May 2007.

To minimize the likelihood of an IOP spike following ECP, it's important to understand the etiology of the problem. There are four main reasons for an IOP spike in this situation: excessive inflammation; retained viscoelastic; excessive treatment; and steroid response. Let's discuss each of these in detail.

• ***Inflammation***. ECP causes some coagulative changes to the tissue, and that incites an inflammatory response. This can be addressed prophylactically, both before and after the procedure. Postoperatively, I always perform a subconjunctival injection of dexamethasone (Decadron), and I slowly taper the topical steroids over a month to minimize any severe inflammatory response. If the patient has significant inflammation or fibrin on postoperative day one, I can augment that with oral steroids for five to seven days. That usually gets rid of any excessive anterior chamber inflammation. You can also transiently increase the topical glaucoma drops regimen and/or add some oral carbonic anhydrase inhibitors such as acetazolamide or methazolamide.

• ***Retained viscoelastic***. This is probably the most common cause of a postoperative IOP spike. When performing ECP, we have to inflate the ciliary sulcus with viscoelastic to give the probe room to reach the ciliary processes. Then, at the end of the case, we have to be very mindful to remove all of the viscoelastic, not just from the anterior chamber (as we usually do) but also from the ciliary


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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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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).

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sulcus. If I have any concern that there may still be viscoelastic left in the sulcus, I'll go in with a cannula and manually inject BSS into the sulcus to make sure I've cleared the sulcus of all viscoelastic.

On postoperative day one, if the IOP is elevated and I believe that residual viscoelastic is the problem, I'll burp the wound, being sure to place a drop of ophthalmic betadine on the area first to minimize the risk of infection. If I've done this two or three times within 24 hours and the pressure still hasn't gone down enough, and extra glaucoma medications don't seem to be helping, I'll consider taking the patient back to the OR to remove residual viscoelastic.

• ***Pigmentary debris from overtreatment.*** Retained pigmentary debris, caused by treating ciliary tissue until it makes an audible pop, can lead to IOP spikes. The popping sound indicates that tissue has exploded, releasing pigment; the pigment debris can then block the trabecular meshwork and cause a rise in IOP.

Obviously, the best way to deal with this is by preventing the explosions in the first place, which can be done by titrating power appropriately. *(See the tips on p. 25.)* However, if you do cause popping, you'll need to spend a fair amount of time performing irrigation and aspiration to clear out the debris. If that happens, you should be aggressive with postoperative steroids; you can give subconjunctival dexamethasone and/or increase the frequency of postoperative topical steroids.

Usually, the pressure will return to normal (or even lower) within five to seven days. Needless to say, prevention is the better approach.

• ***Steroid response.*** IOP can also spike in response to steroid use. Obviously we're being aggressive with steroids after ECP to try to decrease any inflammatory response. As you know, some glaucoma patients are steroid responders. If your patient has a history of steroid response, don't overtreat, and avoid using stronger steroids like difuprednate (Durezol).

When I'm treating a steroid responder, I'll use my regular postoperative regimen—prednisolone four times a day. Sometimes I'll use loteprednol instead of prednisolone, but I'll often augment it with postoperative topical NSAIDs to minimize the postoperative inflammatory response. I taper the patient off the topical steroids as soon as possible.

Other less-common causes of pressure spikes following ECP include:

• ***Aqueous misdirection.*** Aqueous misdirection, or malignant glaucoma, is extremely rare in this situation—I've only seen one case in my career—but it can occur following any type of intraocular surgery, including ECP. Unfortunately, it's easy to miss because we typically consider aqueous misdirection as a process only seen after trabeculectomies or tube shunt implantation. We need to remember that if the patient develops a shallow anterior chamber and elevated IOP postoperatively, aqueous misdirection is a possible etiology.

• ***Cystoid macular edema.*** CME is uncommon following CPC, although it's not as rare as aqueous misdirection. It probably occurs in fewer than 1 percent of patients. Nevertheless, CPC incites a postoperative inflammatory reaction, so the patient has some risk of developing CME—especially if the patient is diabetic. You want to stymie any potential postoperative inflammation as much as possible to minimize this risk.

I minimize the risk by treating prophylactically with subconjunctival dexamethasone, and when I'm going to perform ECP, I treat both preoperatively and postoperatively with topical NSAIDs. If CME does develop postoperatively, I'll increase the topical steroid regimen and I'll seriously consider using sub-Tenon's steroids to ameliorate the edema.

**Micropulse CPC Versus Continuous Wave Transscleral CPC in Refractory Glaucoma**

| | Micropulse TSCPC | TSCPC |
|---|---|---|
| Number of patients | 24 | 24 |
| Preop IOP | 36.5 mmHg | 35 mmHg |
| Average follow-up | 17.5 months | 17.5 months |
| IOP reduction | 45 percent | 45 percent |
| Success rate ( ≤21 mmHg at 12 months) | 52 percent | 30 percent |
| Prolonged hypotony | 0 | 5 (20 percent) |
| Phthisis bulbi | 0 | 1 (4 percent) |
| Mean number of treatments | 1.6 (retreatment rate: 47 percent) | 1.3 (retreatment rate: 46 percent) |

A randomized study of 48 patients with refractory glaucoma, conducted in Singapore, found that both TSCPC and MPCPC were effective at lowering IOP, but MPCPC had a more consistent and predictable effect, with minimal ocular complications.[8]

## Micropulse CPC

The latest iteration of CPC, micropulse cyclophotocoagulation, or MPCPC, minimizes the elevation of temperature inside the targeted tissue by dividing a continuous-wave beam of energy into a series of short pulses. As a result, the targeted tissue cools back down before any coagulation takes place. This has the effect of altering the tissue without

**Safety Profile: Micropulse CPC Versus Continuous-wave TSTCP in Refractory Glaucoma[8]**

| Outcome Measure | MPCPC | TSCPC |
|---|---|---|
| Number of patients | 23 | 23 |
| Number of patients with ocular complications | 20 (88%) | 9 (40%) |
| Prolonged anterior chamber inflammation | 1 (4%) | 7 (30%) |
| Phthisis bulbi | 0 | 1 (4%) |
| Scleral thinning | 1 (4%) | 4 (17%) |
| Visual acuity decline | 1 (4%) | 2 (9%) |

destroying it. For that reason, I like to refer to this as "cyclomodification," rather than cyclodestruction.

This lack of destruction has been demonstrated in several studies. One study reported by Murray Johnstone, MD, at the 2017 meeting of the American Glaucoma Society, found that tissue treated with MPCPC showed no sign of ciliary epithelium coagulative damage or motion. Only subtle changes could be seen upon evaluation.

This raises an interesting question: The traditional assumption about the mechanism of action of CPC has been that it causes damage that prevents the ciliary processes from creating aqueous, thus helping to lower pressure by lessening "input" rather than enhancing outflow. If this version of CPC isn't causing any visible damage, why does intraocular pressure drop after treatment?

The answer may lie in an older study published in 1994.[7] This study found that TSCPC causes enlargement of the extracellular space in the stroma and separation of the ciliary muscles from the sclera. This suggests that the decrease in IOP may have resulted from both reduced aqueous secretion and enhanced uveoscleral outflow. Given that MPCPC minimizes damage to the tissue, this may explain why it's nonetheless effective at reducing IOP.

Here are some pearls for making the most of MPCPC:

• ***Don't hold the P3 Probe the way you'd hold the G-Probe.*** Occasionally, surgeons report a lack of good response to treatment with MPCPC. In my experience, this is usually the result of a simple technique problem involving how the probe is being held against the eye. Surgeons who've used the G-Probe to perform transcleral CPC are accustomed to placing that probe positioned at the limbus, held parallel to the visual axis. Because of the design of the G-Probe, including the off-center positioning of the laser inside the probe and the curved tip designed to hug the globe, this delivers the laser energy to the correct area inside the eye.

The P3 Probe used for micropulse CPC is designed differently. It has a more rounded tip, with the laser coming out at the center, so it should be positioned about 1 mm back from the limbus and held perpendicular to the surface of the globe in order for the laser to treat the correct area inside the eye. If it's held the same way as the G-Probe—which surgeons may instinctively do—the treatment will have little effect. (*See sample pictures, p. 26.*)

The other factor that can cause a surgeon to hold the probe incorrectly is a tight orbit. If there's not much room around the globe, it's challenging to hold the probe perpendicular to the eye, 1 mm back from the limbus. This encourages the surgeon to hold it more like the G-Probe, with the same less-than-excellent results.

Because this misunderstanding about how to hold the P3 Probe is so widespread, when people tell me they're not getting much response to treatment, that's the first thing I tell them to try changing.

• ***When sweeping the probe along the eye, try doing shorter segments at a time.*** When you're sweeping across 180 degrees, the probe tip may get stuck on the conjunctiva, particularly if the ocular surface isn't well lubricated. I prefer sweeping across shorter 90-degree segments; I find the probe tip is less likely to get stuck, making treatment less awkward.

• ***Don't be afraid to use MPCPC in cases of refractory glaucoma.*** Given that micropulse minimizes the tissue damage, surgeons may worry that it won't be effective in refractory individuals. One excellent study looked at that, comparing micropulse CPC to traditional continuous wave diode CPC in 48 end-stage glaucoma patients.[8] The groups had nearly identical IOPs before treatment: 36.5 mmHg vs. 35 mmHg, and both approaches produced a 45-percent reduction in IOP. In fact, in this study the micropulse group had a slightly greater success rate, based on the definition of success used in the study—pressures between 6 and 21 mmHg and a 30-percent reduction in IOP at 18 months. (*See table, p. 23.*)

The only significant tradeoff was a slightly higher retreatment rate. Here it was an average of 1.6 treatments to achieve success, vs. 1.3 treatments for the continuous wave group. (In our experience it can sometimes be more than that. In my practice the mean number of treatments is closer to two, particularly for patients with advanced disease.) So, you're trading a little convenience for the safety and efficacy you gain with MPCPC.

## Three Key Strategies

The following strategies will help

minimize any complications when performing CPC:

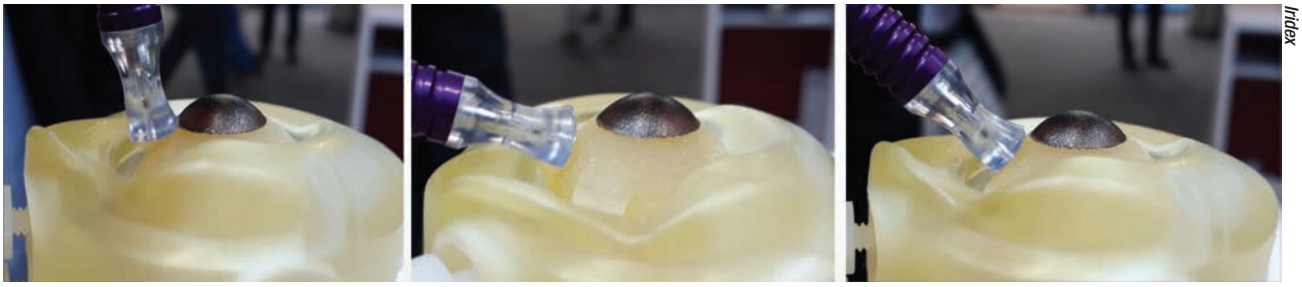
• ***Avoid causing the popping sound.*** The audible "pop" you may hear during TPC or ECP is the sound of tissue exploding. Exploding tissue is never a good thing, so this is something you want to avoid. (You can see ciliary processes popping—on camera—in a video by Craig Chaya, MD's group in Salt Lake City, at youtube.com/watch?v=OKMR3tCenlk. The footage of ciliary processes popping starts about 2:45 into the video.)

*Hopefully, more ophthalmic surgeons will realize the advantages of this approach to lowering IOP—the avoidance of patient adherence issues, the cost-effectiveness, and the benefits for the patient's quality of life, to name a few.*

There are two protocols for avoiding causing the ciliary processes to explode. Historically, surgeons started between 1,750 and 2,250 mW of energy applied for 2,000 mS, and would turn up the power until a little crackle was audible; at that point, you'd back off the power a little bit and proceed with treatment. I would typically perform 12 spots of treatment per hemisphere, skipping the 3 o'clock and 9 o'clock positions (see the explanation below).

However, in the past couple of years I've been using the Gaasterland "slow coagulation technique" which involves starting with a lower power and applying it over a longer duration. Again, I increase power until I hear a little crackle and then treat using slightly less than that amount. This method has resulted in a higher degree of efficacy with a better side-effect profile: less edema; less inflammation; and less discomfort postoperatively. (In either technique the important thing is to avoid reaching the level at which you hear a loud pop. If you hear that, you're more likely to get significant postoperative inflammation, fibrin and possibly even hypotony.)

• ***Avoid performing CPC at the 3 and 9 o'clock positions inside the eye.*** The long, posterior ciliary vessels, including the arteries, typically enter the eye at the 3 and 9 o'clock positions. For that reason, performing CPC at those locations means a higher risk of causing ischemia, hypotony and all of the other negative sequelae that we're concerned about.




Surgeons who've used the G-Probe to perform transscleral CPC are accustomed to placing that probe at the limbus, held parallel to the visual axis *(above, left).* Because of the different design of the P3 Probe used for micropulse CPC, it has to be positioned about 1 mm back from the limbus and held perpendicular to the surface of the globe in order for the laser to treat the correct area inside the eye *(above, right).*

Many surgeons are aware of this and try to avoid these areas when treating, but if the eye has been anesthetized using a retrobulbar block it may cyclorotate, changing the location of 3 and 9 o'clock. (Even without a block, eyes may cyclorotate a little when the patient lies down.) For that reason, I mark the eye at 3 and 9 o'clock preoperatively, to avoid inadvertently treating those areas.

Although I've seen videos in which surgeons using micropulse CPC don't skip the 3 and 9 o'clock sections, I still believe that it's a good idea to skip these locations, even with this less-destructive technology. Theoretically the laser doesn't penetrate as deeply, and it might not hit those deeper vessels, but I'm not going to take that chance. I don't think skipping two clock hours of treatment is going to have a major impact on the outcome, so I err on the side of caution.

• ***When using ECP, be aware that inaccurate placement of the treatment can lead to a refractive shift.*** Not many surgeons realize it, but if you laser the ciliary processes a little too anteriorly, the tissue changes can cause forward movement of the iridozonular complex, resulting in a small myopic shift. Likewise, if you apply the laser a little too posteriorly, the tissue changes can pull the complex posteriorly, causing a small hyperopic shift. If this is happening, it's likely to be a consistent problem, resulting in a consistent refractive shift one way or the other.[9]

Given that we still don't get about 10 percent of our patients within 0.5 D of our target, it's easy to overlook asymmetric ECP treatment as a possible explanation for a slight, consistent refractive surprise. However, if you're performing EPC, there could be a connection. So, try to perform a uniform, diffuse application across the ciliary processes—not too anterior or posterior. Then, be sure to track your refractive outcomes postoperatively and adjust your technique accordingly if you find that your refractive results are a little bit off.

## A Valuable Option

Today, doctors treating glaucoma are more comfortable using CPC earlier in the treatment course than they were in the past. I think this is true for two reasons: First, surgeons younger than 45 have seen their attendings use CPC earlier in the course of the glaucomatous disease process, with good results. Thus, they feel more comfortable incorporating it earlier in their treatment paradigm. The second factor increasing the use of CPC is the arrival of micropulse CPC. This has shifted the risk/benefit ratio even more in the direction of safety, and that makes surgeons more comfortable about using CPC earlier in the game.

Hopefully, more ophthalmic surgeons will realize the advantages of this approach to lowering IOP—the avoidance of patient adherence issues, the cost-effectiveness, and the benefits for the patient's quality of life, to name a few. In terms of outcomes, close attention to detail, as well as taking advantage of some of the pearls provided here, should prevent untoward complications and ensure excellent results. REVIEW

*Dr. Kammer is an associate professor of ophthalmology at Vanderbilt Eye Institute in Nashville, Tennessee. He has consulted for Allergan, Aerie, Iridex and New World Medical.*

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# Refractive Surprises: What To Do Next

*Christopher Kent, Senior Editor*

Surgeons offer advice for those times when your cataract surgery outcome isn't on target.

When performing refractive cataract surgery, a perfect outcome is always the goal, and the number of patients hitting their refractive target has increased steadily over the years. However, the challenges inherent in operating within a complex, living system have kept the success rate from reaching 100 percent. As a result, surgeons still have to deal with cases of postoperative refractive surprise.

"Tools such as intraoperative aberrometry and better power calculation formulas, like Hill RBF and Graham Barrett's formulas, have made refractive misses less common," notes John Berdahl, MD, a corneal, refractive and glaucoma surgeon at Vance Thompson Vision in Sioux Falls, South Dakota, and associate clinical professor at the University of South Dakota. "Nevertheless, today we still enhance 10 to 15 percent of our patients that have a refractive endpoint in mind."

William B. Trattler, MD, director of cornea at the Center for Excellence in Eye Care in Miami, and a volunteer faculty member at the Herbert Wertheim College of Medicine at Florida International University, agrees. "Refractive surprises are definitely less frequent, but they still do happen," he says. "Premium IOL patients, in particular, have high expectations. They want to end up on-target."

When a patient's outcome isn't what was hoped for, the surgeon has to make a number of decisions. Is the refractive miss significant enough to require correcting? What, exactly, is the cause of the less-than-ideal outcome? And if I'm going to correct the refractive result, which method makes the most sense for this patient?

## Should You Correct It?

"Not all refractive misses have to be surgically corrected," notes Dean Ouano, MD, a cornea and anterior segment specialist at the Coastal Eye Clinic in New Bern, North Carolina. "Despite advances in optical biometry and IOL formulas, a significant percentage of patients fail to achieve emmetropia. If you look at the Swedish National Registry study published in 2012, 17,000 patients were targeted for emmetropia in cataract surgery, but only 55 percent of them actually achieved it.[1] So deciding to correct a refractive surprise is a question of degree. The patient has to be symptomatic, and the refractive miss has to be large enough to justify surgical intervention.

"Deciding to explant or exchange a lens shouldn't be done lightly," he continues. "Before you surgically in-



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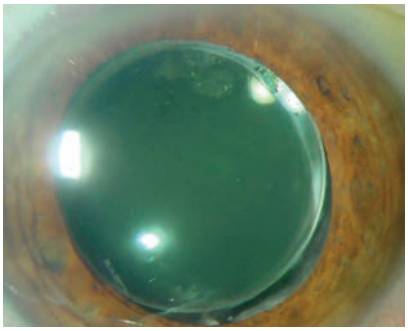
tervene in a refractive miss you have to figure out several things. How big is the miss? Will the patient tolerate the residual refractive error if it's corrected by spectacles or contact lenses? Have you ruled out any other coexisting problems such as macular disease, ocular surface disease or irregular astigmatism? I think each case has to be examined on its own merits."

To be certain that you really do need to make a refractive adjustment, surgeons emphasize two points: First, make sure you understand exactly what's causing the refractive issue. Second, make sure to wait an appropriate amount of time before drawing any final conclusions about the size of the miss.

"There are a couple of things you need to check out," says Dr. Berdahl. "Is there other pathology going on, such as posterior capsule opacity or a retinal problem? Is the lens tilted? Also, keep in mind that some problems can't be corrected by adjusting the refraction. Let's say you implanted a bilateral extended-depth-of-focus lens and the patient's main complaint is inadequate near vision. Adjusting the refraction isn't necessarily going to solve that problem. You need to understand the nature of the problem before you try to solve it."

Bryan Lee, MD, JD, in private practice at Altos Eye Physicians in Los Altos, California, agrees that sometimes the nature of the IOL is the problem. "If the patient's unhappy after you put in a multifocal or extended-depth-of-focus lens, one of the things you have to figure out is whether the problem is residual refractive error or an optical problem relating to the IOL design," he says. "Figuring that out may require having the patient wear a pair of glasses or contact lenses to make sure they're actually happy when the refractive error is corrected. If they are, then laser vision correction makes sense. The main point is that you have to figure out exactly what's making the patient unhappy."



Dean Ouano, MD

A piggyback IOL is sometimes a good choice for correcting a refractive surprise, but anatomical issues always need to be considered. Here, the sharp edge of the optic is causing pigment dispersion.

Surgeons also agree that in most cases it's crucial to wait before making a final determination about the extent of a refractive miss. "I won't usually make a refractive miss call until three months after surgery, when I feel sure the eye is entirely stable," says Dr. Berdahl. "You're probably on reasonably safe ground if you decide as early as three weeks out, but I want the next move I make to be definitive. For that reason, I prefer to wait at least three months for the refraction to settle."

"It's important not to make that decision too early," agrees Dr. Lee. "You need to give the patient at least a couple of weeks to be refractively stable, and some patients may need even more time to get where they're supposed to be. You don't want to correct something prematurely."

## Minimizing Alternate Factors

Given that issues besides a refractive power miss can affect vision, and additional surgery should ideally be avoided, you can take several steps to ensure that a surgical adjustment is really necessary.

"One of the things that impacts the final refractive outcome is the ocular surface," notes Dr. Trattler. "Many patients have mild dry eye or meibomian gland dysfunction before surgery, and those can be worsened by all the drops associated with surgery. That can impact postoperative quality of vision and the refractive error. Eyecare providers can focus on reducing postoperative inflammation, and at the same time treat the underlying ocular surface condition.

"The impact of a condition such as dry eye may not be that obvious, but you'll be surprised when you treat postoperative patients for dry eye," he continues. "Some patients may improve enough that they won't need further surgery to improve their vision—even though you thought they did. For example, let's say you have a patient who is 20/30 with -0.75 D of cylinder. The patient may say, 'My vision isn't what I expected.' While one might believe the patient's complaint is due to the small amount of residual astigmatism, further questioning may reveal that it's actually the result of fluctuating vision caused by dry eye. In my experience, treating dry eye can eliminate 60 to 70 percent of the patients who initially seem to need an enhancement following cataract or lens replacement surgery.

"Make no mistake, patients don't want to undergo more surgery, so they'll be happy if you can resolve the problem without it," he says. "That's why if the patient is unhappy, my protocol is to first treat for dry eye and meibomian gland disease, even if these conditions aren't obvious. Increasing tear quality—even if it wasn't terrible before—can significantly improve their vision."

Dr. Berdahl agrees. "The first thing to examine and treat is the ocular surface," he says. "Whatever target you're shooting for, you don't want it to be a moving target. As we all know, dryness and ocular surface disease are common in these patients, and those conditions can affect the refraction. If the ocular surface isn't OK, then we need to treat it and rehabilitate it."

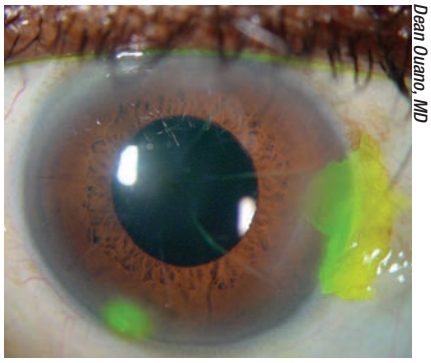
Dr. Trattler says a second concern

is that mild posterior capsular opacification can also impact quality of vision. "Sometimes if we laser the capsule, vision is improved just enough to eliminate the problem," he says. "The lens may even shift a little bit, changing the refractive outcome a little and improving vision. In some borderline cases, this may avoid any need for fine-tuning." With this in mind, Dr. Trattler says he routinely performs a YAG when a patient is unhappy with the outcome and he's planning a refractive surgery enhancement. "Of course, I don't charge for this because I'm not treating something that's causing a loss of best corrected visual acuity. But this protocol sometimes makes a real difference.

"The other thing that can happen is, let's say you don't YAG and you perform laser vision correction," he continues. "Three months later the patient's PCO worsens and they experience capsular contraction, which can shift their refractive error. If you've performed a YAG prior to the laser vision correction, the vision is a little bit more stable long-term. Skipping the YAG would be quicker, but we work through all of these steps to make sure we really optimize the patient's vision. Again, you can't charge insurance for this without the presence of significant PCO, and I wouldn't charge the patient either. I just include it as part of the refractive fee because I want to optimize the patient's vision.

"If you do both things—treat the ocular surface and perform YAG—many patients will be happier with their postoperative visual outcomes," he concludes. "That's the protocol I like to follow before moving on to surgical enhancement."

Dr. Trattler explains how this works in terms of timing. "Once it's clear that a patient is unhappy with his vision following surgery, we first finish the course of postoperative drops and get him through the first month," he says. "Then we see how he's doing and re-



Dean Ouano, MD

Patients with prior radial keratotomy may be more likely to end up with a refractive surprise following cataract surgery. Above: A postop cataract patient with prior RK and ReSure tissue adhesive on the wound.

refract. If he's still unhappy, then we'll try to optimize the ocular surface. We initiate dry-eye therapy; if it appears to be meibomian gland disease, we'll treat with warm compresses, antiseptic sprays for the eyelashes and often a three-week course of a topical steroid. In cases of aqueous-deficiency dry eye, we often start a topical steroid, along with either Restasis or Xiidra, and we may also place punctal plugs. Then we give the patient another month. When the patient returns, we re-refract. We also check the posterior capsule. At two to three months we may do a YAG capsulotomy. After another week or two we check everything again.

"At this point the refraction is relatively final," he concludes. "This protocol gives the eye time to heal and adjust, and often things have improved enough that the patient is happy. If so, no further correction is necessary."

## Should You Use the Laser?

When choosing a way to adjust the refraction, if you've decided that a correction is necessary, the choices can be broadly divided into two categories: IOL-based changes—i.e., replacing the IOL or adding a piggyback lens—and laser refractive procedures.

Deciding whether or not to proceed with corneal laser surgery requires considering numerous factors:

• ***The size of the adjustment.*** Dr. Ouano says that if the patient's spherical error is more than 4 D off in either direction, you should avoid using laser surgery to make a correction. "I think most surgeons would agree that a large refractive miss calls for an IOL-based solution," he says. "For example, a +4 D hyperopic keratorefractive procedure on an older patient is generally not a good idea. On the other hand, a smaller refractive miss is a gray zone. If the patient is a -2 D myopic miss, you have a lot of options."

• ***The direction of the adjustment.*** "Another thing to take into account is the direction of the refractive error," notes Dr. Lee. "Lasering someone who is -1 D is easier and more accurate than lasering someone who is +1 D off-target."

• ***Accuracy.*** "A 2013 study in the *Journal of Refractive Surgery* showed that laser refractive surgery is able to more accurately correct residual astigmatism and refractive errors than an IOL exchange or a piggyback lens," notes Dr. Ouano.[2] "That makes sense, because LASIK and PRK were designed to be accurate. For example, suppose your miss is -3 D sphere and -2 D cylinder. An IOL exchange isn't going to be very reliable for correcting the cylinder, but a LASIK or PRK procedure could be. In addition, you'd avoid another intraocular procedure."

• ***Age of the patient.*** "The patient's age has to be considered, because a 75-year-old undergoing LASIK has a much different healing process than a 25-year-old," notes Dr. Ouano. "Older patients have more ocular surface disease and dry eye."

Dr. Lee agrees. "Cataract-age patients are older, and they often have a worse ocular surface," he says. "You have to consider how dry the eyes are and how easily the patient will recover from refractive surgery."

• ***Prior laser refractive surgery.*** "If the patient has had prior LASIK

or PRK, I typically wouldn't want to do further laser correction on that patient," says Dr. Lee. "Doing PRK over a LASIK flap is less accurate. So in general, if the patient has had laser refractive surgery I'll do a lens exchange. I think it's more accurate in that situation."

• ***Contraindications***. Performing LASIK or PRK on a patient under any circumstances requires that the cornea meet appropriate specifications. "You have to consider the normal contraindications for LASIK or PRK—things like corneal thickness and keratoconus," Dr. Ouano points out.

• ***Practical issues, including access to the technology.*** "Logistics, availability and reimbursement are all issues with PRK and LASIK," says Dr. Ouano. "For one thing, not every office has access to an excimer laser."

Dr. Lee agrees. "If you don't have access to an excimer laser, that may push you towards doing an IOL exchange or piggyback in these situations," he says. "On the other hand, if you operate in a hospital setting and the cost of doing an IOL exchange is outside of your control, that might push you towards doing an excimer laser treatment. Either choice is probably fine, because clinically, one way isn't necessarily better than the other."

Dr. Berdahl says he believes residual refractive error is probably undertreated in general, simply because many surgeons don't have access to an excimer laser. "If you don't have access to a laser, you should consider developing a relationship with someone in your community who does," he says. "Try to work out a system where you either can use their technology, or they'll do enhancements on your patients for you."

## LASIK or PRK?

If an adjustment by excimer laser seems like the best choice, the next question is whether to opt for LASIK, PRK or another procedure such as SMILE.

"If the patient ends up on the myopic side, I typically perform laser vision correction," says Dr. Trattler. "We don't have access to SMILE, but we perform both LASIK and PRK—mostly PRK, although LASIK is certainly an option for myopic or astigmatic fine-tuning." Dr. Trattler uses epi-Bowman's keratectomy, performed with a device called EpiClear (ORCA Surgical), which removes the epithelium and collects discarded cells into its tip without touching Bowman's membrane. Dr. Trattler says that in his experience this is more comfortable for patients than traditional epithelial debridement with alcohol.

Dr. Berdahl says he prefers to do a refractive correction with LASIK rather than PRK. "I think the results are a little bit better in an older population," he says. "Because these patients are older, their epithelium can be more irregular. Doing a low-correction PRK can unmask that irregular epithelium, leading to more variable results. In fact, epithelial mapping can be very helpful when trying to decide whether you should do LASIK or PRK.

"It's kind of a conundrum," he continues. "If the epithelium is very irregular, that might indicate anterior basement membrane disease, which probably should have been treated prior to cataract surgery. But if you're faced with a very irregular epithelium postoperatively, you should do a superficial keratectomy or phototherapeutic keratectomy and see how it heals; then come back and do LASIK or PRK. If the epithelium is mildly irregular, which is true for a lot of patients, then I'd probably do LASIK. I don't want to unmask that irregular epithelium with PRK, causing it to be translated into the refractive outcome. If the patient has a very regular epithelium, than either LASIK or PRK is OK.

"I think an irregular epithelium is one of the things that cataract sur-

## Accommodating the Patient

Whatever course of action you choose—including not making a refractive adjustment at all—will depend partly on the patient's satisfaction and comfort with your preferred method for making a correction. "Assuming that you've got a stable refraction—you've treated the tear film and the ocular surface looks OK—patient happiness is an important consideration," says Bryan Lee, MD, JD, in private practice at Altos Eye Physicians in Los Altos, California. "This is especially true when the patient has elected to have some type of refractive cataract surgery, whether that's astigmatism correction or presbyopia correction. Perhaps you implanted a toric IOL, aiming for plano, but the patient ends up at -0.75 D. It's possible that the patient will be happy in spite of that, and I wouldn't do anything if the patient is happy.

"However, there are times when I'll tell the patient that this is something we should probably adjust, because there's a time-window for fixing things," he continues. "Let's say I've implanted a toric lens and it's not in the ideal position to correct his astigmatism. Sometimes the patient is happy anyway, but my astigmatism calculator tells me his vision would be significantly better if I rotate the lens a little bit. In that case, I'd suggest to the patient that we make the correction and not wait to see how it goes over time. If we wait, the capsule will contract around the IOL and rotating the lens will become much more challenging."

Dr. Lee notes that the decision to rotate an IOL is relatively easy in some situations. "Let's say you're seeing a patient between the first and second eye," he says. "You know you can position the toric lens in the first eye better, and you're going to be in the OR anyway to do the second eye. It makes sense to tweak the first eye while you're there. It doesn't inconvenience the patient at all, and typically there wouldn't be any additional charge to the patient. In that scenario in particular, I'd be more likely to recommend tweaking or adjusting the IOL position, even if the patient is pretty satisfied."

John Berdahl, MD, a corneal, refractive and glaucoma surgeon at Vance Thompson Vision in Sioux Falls, South Dakota, says he's careful if he gets a positive patient reaction when he knows a refractive miss has occurred. "If patients say they can do everything they want to do easily and without annoyance, then I may agree that the goal has been achieved and leave well enough alone," he says. "But if a happy patient indicates any sign of difficulty at all, then I'll say, 'I think I can make you even happier.' I'll make sure the patient knows that improvement is possible. So it's not just '20-happy' for me. If I know I can improve the patient's vision further, it's my obligation to inform them of that and help them make the best choice."

*—CK*

geons frequently miss," he adds. "It's easy to overlook. I think it's one of the main reasons surgeons have some dissatisfied patients after receiving a refractive IOL and an enhancement."

What about using SMILE? "I think it's too early to tell whether SMILE will be great for refractive enhancements," says Dr. Berdahl. "What we like about SMILE is that perhaps there's a little less postoperative dryness—although that may be debatable. The biggest concern with using SMILE to correct a refractive miss is that these are usually very small corrections. Removing a very small SMILE lenticule can be challenging.

"Nevertheless, I think SMILE holds a lot of promise for all things refractive, including enhancements," he says. "SMILE is a very young procedure, and we're going to get better at using it as time goes by."

## Laser or IOL-based Correction?

Alternatives to laser refractive correction include an IOL exchange or adding a piggyback lens. Several factors—surgeon preference among them—determine whether an IOL-based change will work better than a corneal laser correction.

Dr. Berdahl observes that some surgeons prefer to go right to an IOL exchange. "That's reasonable if you're facile with IOL exchanges," he says. "That approach can give you good results." However, Dr. Berdahl says that when he's considering whether or not to exchange the IOL, corneal stability is a major concern. "If it's a post-RK patient, I won't have good laser-refractive-enhancement options," he notes. "In that situation, I think IOL exchange makes the most sense. That may be true for post-LASIK patients, too, if I'm not comfortable dealing with a previous LASIK flap. Of course, many surgeons don't have access to an excimer laser, so they'll do an IOL exchange simply because they don't have the other option. But if all else is equal, I think in most cases the excimer laser is the most precise way to correct a refractive miss."

Sometimes if a patient isn't eligible for the specific laser procedure the surgeon believes will be easiest for the patient, that's sufficient to cause a shift to an alternative such as IOL exchange. Dr. Lee says that if a patient is a candidate for PRK but not LASIK, he may decide to perform an IOL exchange. "The patient will have a more comfortable and faster recovery with IOL exchange than PRK in many cases," he explains.

Dr. Ouano says his approach in this situation would depend on the patient's overall refractive error. "If it was a very large spherical miss, I'd go with a lens exchange, as long as the lens hasn't been in there too long," he says. "In early lens exchanges, the bag is more pliable and amenable to exchange."

## Piggyback or Lens Exchange?

If laser correction is off the table,

should you opt for exchanging the IOL or adding a piggyback lens?

"A straightforward lens exchange is appealing to me, because you're going to maintain the desired anatomy of the eye—switching an in-the-bag lens for an in-the-bag lens," says Dr. Ouano. "You're not going to have two lenses inside the eye, and you're not going to disrupt the corneal surface. You can usually use the same entry wound, and it's a straightforward, safe surgery if it's done in the early postoperative period, as long as you have an intact rhexis and intact posterior capsule and zonules. An early IOL exchange for a refractive miss after cataract surgery, is, in my opinion, a good procedure. Furthermore, in our experience, the reimbursement pathway for an IOL exchange after a refractive miss is also straightforward. So if there's a refractive miss following cataract surgery my preference is to do an IOL exchange during the early postoperative period."

Dr. Ouano says he doesn't favor the piggyback option, although some surgeons in his practice prefer it. "I understand why they like it," he says. "Number one, it's technically easy to do. Two, selecting the lens implant is easy to do because it's based on the postoperative refractive error. Three, the reimbursement pathway is reasonable. The financial barriers are not as insurmountable as they can be if you do a LASIK procedure on a 75-year-old patient. So the piggyback option has some advantages.

"However, I think the disadvantages are also significant," he continues. "The patient might have a very shallow anterior chamber, in which case there's a real possibility of iris chafing, pigment dispersion or UGH syndrome. And a big downside is that we don't have a lot of choices for a sulcus-fixated IOL in the United States. We currently have two silicone three-piece lenses for the plus powers: the Bausch + Lomb Sofport LI61AO and the Tecnis Z9002. There are minus-power lenses from Johnson & Johnson Vision within a certain range. But the lack of an ideal sulcus-fixated IOL is a disadvantage for the piggyback option.

"The biggest problem," he adds, "is that if you have a large myopic miss—let's say -9 D—you're not going to solve that with LASIK or PRK, and you can't get an IOL that high. You can use an implantable contact lens off-label; they come in powers up to -16 D. But it raises a big financial issue: Who pays for the ICL? It's quite a bit more expensive than a standard IOL. So piggybacking in that situation isn't a good option."

Dr. Ouano admits, however, that if you're contemplating a lens exchange instead, timing is a major concern. "Opening a capsular bag late, let's say six months to a year after the surgery, is more difficult," he notes. "There are risks involved, depending on the status of the zonules and the posterior capsule, so exchanging the lens isn't necessarily a slam dunk. It's not impossible, but it's more difficult to manage."

Dr. Lee says that in his experience implanting a piggyback lens usually works well. "Calculating the power is straightforward, and the procedure is straightforward as well," he says. "However, not every patient can tolerate a piggyback lens, depending on the anatomy of the anterior segment. That's not totally predictable, so if you put in a piggyback IOL, sometimes it will have to come out later. If I'm planning to use a piggyback lens, I'll always mention preoperatively that occasionally these piggyback lenses have to be explanted. Fortunately, it's very straightforward to remove a piggyback IOL.

"I think in general a piggyback lens is a good way to correct refractive error," he continues. "Again, it depends on the clinical situation. You might have a patient with bad zonules, or one who's uncooperative during the

surgery. Factors like these might push you towards thinking about implanting a piggyback lens instead of performing an IOL exchange, but the anatomy will still be a factor. Just a few weeks ago I had a patient who'd had prior LASIK and was off-target. That patient had already had a YAG laser, so I didn't want to laser or do an IOL exchange. I did a piggyback, and he's done very well so far."

Dr. Trattler says he doesn't often exchange IOLs. "If the patient's hyperopic, I prefer to implant a piggyback lens," he says. "Implanting a piggyback lens is very simple. You make a tiny incision, insert the lens, put Miochol in the eye, and you're done. It's very fast and patients have very good outcomes. In contrast, if you have to free-up an IOL, bring it into the anterior chamber, bisect it with scissors inside the AC, remove the IOL fragments and then place a second lens inside the capsular bag, there's a little more surgery and risk. Of course, you may have to perform an exchange if you implanted a toric lens with the wrong astigmatic power, or the patient is unhappy with the glare and haloes caused by a multifocal lens. But if everything's fine other than the patient being a little hyperopic, then a piggyback lens can work very nicely."

Dr. Trattler adds, however, that he generally reserves the piggyback option for refractive surprises that are significantly hyperopic. "For myopia, PRK and LASIK are very effective," he says. "If we're talking about 1.5 D of hyperopia or higher, laser vision correction has been a little underwhelming. Of course, if it's a hyperopic refractive surprise of 0.5 or 0.75 D, then LASIK or PRK is fine. But if more than 1 D of treatment is needed, I'll typically use a piggyback lens."

## Some General Advice …

Surgeons offer these suggestions to help things go smoothly:

• ***First, let the patient know you're on the case.*** "When you have a refractive surprise, be sure the patient knows that you care about this, and that you're going to work to get them where they want to be," says Dr. Berdahl.

• ***Don't shy away from rotating a misaligned toric IOL.*** Dr. Lee notes that whether or not a toric lens rotational adjustment should be made in a borderline case depends on numerous factors. "If someone has a very high-powered toric lens implanted, like a T6, and the lens is 7 degrees off, that patient's vision will be affected a lot more than a patient who has a T3 lens but is rotationally further off-target," he says. "So it depends on the clinical situation—as well as the patient's personality.

"I know that some surgeons hesitate to go back in to rotate a toric IOL," he adds. "Aside from having to re-enter the eye, you're telling the patient that you want to take him back to the OR, and there could be a cost associated with it, depending on whether you operate in a hospital or in a surgery center where you have more control. But surgically it's not too difficult to rotate a lens, as long as you're doing it within three or four weeks after the initial surgery. It's pretty straightforward, and it can help the patient."

• ***Keep the lines of communication open.*** "Be sure to continue to communicate with the patient postoperatively, especially if the patient is unhappy," says Dr. Lee. "You have to take the initiative to follow-up and keep the communication lines open so you have as good a relationship as possible."

• ***Perform a trial correction before proceeding.*** "Before I actually perform the procedure, whether it's PRK, LASIK or a piggyback lens, I typically have the patient undergo a contact lens trial to demo what their corrected vision will be like," says Dr. Trattler. "Patients often assume that altering the outcome won't change the parts of their visual outcome they already like, which isn't the case.

"For example, let's say we have a patient who ends up a little on the nearsighted side," he continues. "They have good computer vision and reading vision, but they want better distance vision. I'll have them demo a contact lens to make sure this change in their vision is really what they want, because if they realize what the trade-off is—getting better distance at the expense of near—they may decide they don't want to have the refractive outcome adjusted after all. That's why a contact lens trial prior to performing an enhancement is helpful. That trial educates the patient about what to expect."

"When the patient has a presbyopia-correcting IOL, I wouldn't make any decision about how to proceed without correcting the refractive miss first," says Dr. Lee. "This can be done with a pair of glasses or contact lenses. I've had many unhappy patients referred to me two or three months after surgery who had never tried a pair of glasses. That's kind of the first step in figuring out what to do: Correct the residual refractive error. Sometimes if you give them a pair of glasses they're so happy they can see clearly that they don't want anything else. And if they still want to have their refractive error corrected, this gives you confidence that the thing that's making them unhappy really is the refractive error."

Sometimes the refractive miss is very small, but the patient is still unhappy. "Suppose a patient ends up +0.25 -0.5," says Dr. Berdahl. "The first thing I want to do in that situation is simulate the adjustment I'd be making, using glasses or contact lenses. The glasses might take the patient from 25/25+1 to 20/15 solid. The patient may put the glasses on and say, 'Yes, this is what I want.' In that case, I'll do the enhancement. But I want to

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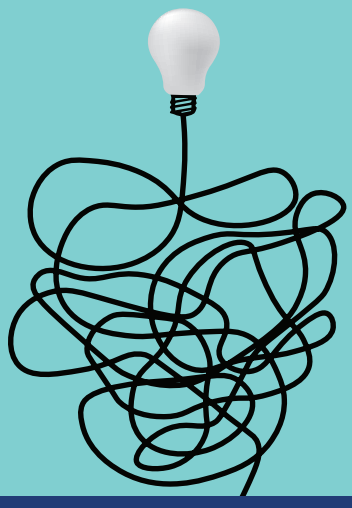

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# Refractive Surgery for Patients over 50

Sean McKinney, Senior Editor

You may now be grappling with one central question for this group: lens- or cornea-based refractive surgery?

Your fastest growing patient population and the field of refractive surgery are reaching their prime at the same time. With more surgical options available than ever, more patients over the age of 50 are flooding ophthalmology practices, seeking new ways to correct presbyopia and other refractive errors.[1] This growing trend has established a paradigm shift in preoperative planning. Increased screening takes precedence over promoting the benefits of LASIK, LASEK, Epi-LASIK, bladeless LASIK, wavefront LASIK, PRK, corneal inlays, implantable lenses and clear lens exchange.

"More than ever, we need to ask ourselves one simple question," says George Waring IV, MD, FACS, founder and medical director of the Waring Vision Institute in Mount Pleasant, South Carolina. "What makes more sense–addressing the cornea or the lens?"

In this report, experts discuss the best answer to this question for a variety of patient types.

## Ruling Patients In or Out

Surgeons accustomed to routine screening of younger patients need to evaluate more factors when individualizing refractive surgery recommendations for patients over 50.

David R. Hardten, MD, FACS, who is in private practice at Minnesota Eye Consultants in Minneapolis, looks carefully at health histories. For example, increased risks of early cataracts could raise second thoughts about refractive surgery for these patients. The following are such risk factors: history of smoking; diabetes; asthma; chronic bronchitis and cardiovascular disease. Inhaled and oral corticosteroids, oral chlorpromazine and oral multivitamin/mineral intake add to the risk.[2]

He also aggressively treats dry-eye disease before considering refractive surgery. "Ocular surface disease is more common in the older patient," he notes. "It will get worse year by year, even after refractive surgery. Helping patients understand this is important."

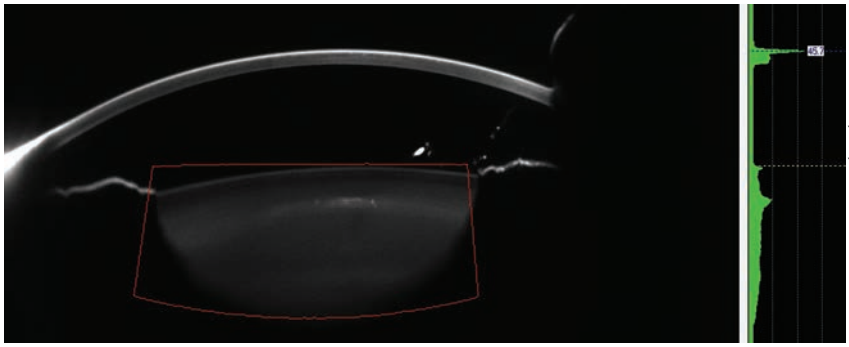
William D. Wiley, MD, medical director, Cleveland Eye Clinic and Clear Choice LASIK Center, holds off on LASIK and SMILE in the presence of contraindications commonly found in the over-50 population. "We won't go through with it if a patient has keratoconus, age-related macular degeneration, corneal scars, early signs of cataract, acute eye disease and other contra-



*This article has no commercial sponsorship.*

indications, such as unstable refractive values, astigmatism over 5 D, suspicious corneal topography and thinner-than-average corneas."

Dr. Wiley emphasizes scrutinizing the lens, the progression of nuclear sclerosis, and the condition of the cornea. "The cornea might not be in the best shape for refractive surgery," he notes. "They could have other conditions, such as Fuchs' endothelial corneal dystrophy, Salzmann's nodular degeneration, pterygium and corneal stromal fibrosis. We need to get any disease under control before proceeding with refractive surgery. Some may require chronic treatment. Others, such as nodules, can be treated [before surgery], allowing us to stabilize the underlying condition and proceed with refractive surgery."



David R. Hardten, MD, FACS

This Pentacam scan shows moderate nuclear sclerosis, which should be closely evaluated along with other factors when deciding whether LASIK or other corneal procedures are worth performing on a patient over 50, say physicians.

## "Younger Elderly Patients"

An increasing number of baby boomers and Generation X patients want visual improvement that will help keep them gainfully employed, attractive and vital well into their senior years. By 2020, an estimated 1.4 billion people will turn presbyopic across the world.[3] And the number of patients in need of ophthalmic care will increase markedly during the next 20 years, primarily because of the aging of the U.S. population.[4]

Alan Aker, MD, who runs the Aker-Kasten Eye Center with his wife, Ann Kasten, MD, in Boca Raton, Florida, has always attracted seniors in need of cataract surgery. Now, he has noticed increased demand for "premium solutions with specific refractive outcomes" expressed by "our younger elderly patients."

He and Dr. Kasten offer lens-based refractive procedures, and they say they've achieved success using the femtosecond laser. The addition of the femtosecond laser has helped the husband-and-wife surgical team increase their percentage of premium cataract-refractive cases from 30 percent to more than 75 percent in recent years. Dr. Aker explains that the femtosecond laser is attractive to the over-50 set because, among other things, its precise, bladeless cutting minimizes postoperative cornea issues and allows for correction of corneal astigmatism.

"For patients of this age who are interested in LASIK, we go into a lengthy discussion of the impact of LASIK and cornea-based refractive surgery on their future cataract surgery," says Dr. Aker. "We explain that following a LASIK procedure, the calculations for the appropriate IOL power can be more challenging."

Dr. Aker also informs over-50 patients seeking LASIK that, after some LASIK procedures, because of resulting spherical aberration, they may not be good candidates for some of the more advanced presbyopia-correcting implants. "We also explain to these younger patients presenting with minimal lens changes that youth and technology are on their side. We are currently involved in an FDA study evaluating the investigational SC9 IOL produced by the CORD Group LLC (Hammond, Louisiana). This is an extended-depth-of-focus IOL. We explain to these patients that this and other new advanced IOLs are currently being evaluated that might be able to provide even better vision than IOLS that are currently approved. Sometimes it's best to wait. We feel it's important to share this option with our patients."

## The Refractive Gamble

Uncertainty can be a challenge when caring for these patients. Some surgeons feel like they need a diagnostic crystal ball of sorts to determine if a refractive procedure after age 50 might actually be too close to a patient's eventual cataract surgery. "These days, I do see too many patients who have had refractive surgery only a year or two before they come to us in need of cataract surgery," says Dr. Aker. "It would seem that lens-based refractive surgery would have been a better choice for them. First of all, lens-based surgery spares the patient the expense of a LASIK procedure. In addition, it leaves the patient with a pristine, untouched cornea, enabling us to provide them with the best possible outcome following cataract-refractive surgery with the appropriate premium IOL."

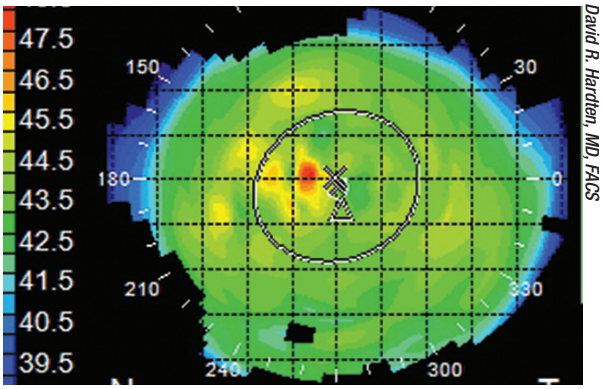
Dr. Hardten evaluates every factor when deciding if a patient is too close to needing cataract surgery.

"When we analyze the lens, including the amount of nuclear sclerosis, we try to figure out if the refractive error will stay the same long enough before cataract surgery is likely needed to make it worth doing corneal refractive surgery alone," says Dr. Hardten.

Dr. Wiley assesses a patient's presbyopia, nuclear sclerosis, possible onset of cataracts and changes in the crystalline lens that begin before and during presbyopia.

"If the patient has experienced a myopic shift, that can be a significant factor," he adds. "Patient history over time is critical."

Dr. Wiley also uses the HD Analyzer (Visiometrics; Terrassa, Spain), which identifies subclinical cataracts by evaluating light scatter, helping determine if cornea-based or lens-based procedures are best. The instrument also measures tear-film breakup time. "We can determine if dry-eye therapy is best or, possibly, if a corneal approach should be avoided because of dry eye," he points out.



David R. Hardten, MD, FACS

This corneal topography map shows signs of epithelial basement membrane dystrophy, a common finding in patients over 50 which requires treatment before refractive surgery.

## Inside Versus Outside

Deciding whether to surgically correct a patient's vision inside or outside of the eye is a judgment call, according to Dr. Wiley. "I base my decision on diagnostics and a big-picture analysis of the patient's visual needs, corneal health and overall health. It's never an automatic yes or no answer."

Deciding whether to address the cornea or crystalline lens involves a multifactorial decision-making process, guided by stages of dysfunctionality, according to Dr. Waring. He has evaluated the aging changes of the crystalline lens over the years. In an attempt to characterize these changes, Dan Durrie, MD, and Jason E. Stahl, MD, both of Durrie Vision in Overland Park, Kansas, and Dr. Waring suggested the term Dysfunctional Lens Syndrome, staged as follows:

***Stage I:*** The lens becomes more rigid and less flexible, corresponding with presbyopia.

***Stage II:*** Contrast sensitivity loss, increased higher-order aberrations and light scatter emerge.

***Stage III:*** Lens opacities are now significant enough to interfere with daily activities. This stage corresponds with cataracts that qualify for an insurance-based procedure.

"We have found that lens replacement in patients with Stage II DLS improves vision in ways LASIK can't," he says. "We can reduce light scatter, improve retinal image quality and maintain binocularity. Furthermore, we are preventing the eventual degradation process into a cataract, when a second intervention could occur. Simply stated, we are preventing cataracts." Dr. Waring still utilizes LASIK or implantable contact lenses "in the high axial myope with peripheral retinal pathology and other risk factors for retinal detachment in patients over 50 in Stage I DLS and, in select cases, in Stage II."

One surgical option for presbyopia is the insertion of the donut-shaped Kamra (CorneaGen, Seattle) corneal inlay in the front of the cornea. The inlay, made of a dark polyvinylidene fluoride, is 3.8 mm in diameter with a 1.6-mm aperture. The Kamra relies on a pinhole effect to enhance near vision, allowing only central rays of light into the visual system to enhance depth of focus. It's designed for monocular implantation at a minimum depth of 200 µm via a femto-created stromal pocket in the non-dominant eye. "If the patient's lens is clear, ages 50 to 55 is the sweet spot for Kamra, providing enhanced range of focus for emmetropic presbyopic patients," says Dr. Hardten. "If the patient has a refractive error of about -0.5 to -0.75, he or she can additionally gain some extra distance while improving near vision."

Dr. Wiley combines Kamra inlays with LASIK for presbyopic patients. "We can target the dominant eye for plano and the non-dominant eye for -1 D," he says. "We insert the inlay to extend the intermediate vision and conceivably remain in there indefinitely, offering a full range of focus of up to 2.5 D."

Dr. Waring is also involved with a number of emerging presbyopia treatments beyond lens technology and excimer lasers, such as presbyopia eye drops. Furthermore, allogenic corneal inlays from corneal tissue are also being evaluated.

## When Age Isn't a Factor

Unlike some surgeons, Dr. Wiley says a patient's older age doesn't always prompt him to take a cautious approach to the corneal surface.

"We do LASIK and SMILE all the time," he says. "On younger patients, we know they also will need

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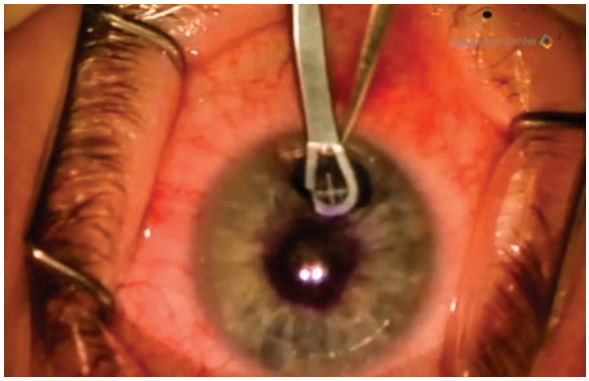
cataract surgery at some point. A 20-year-old is the same as a 55-year-old, as I see it. Both have the same risks."

Like many surgeons, Dr. Wiley is hardly an absolutist. "If I clearly see a patient is a year away from needing a cataract extraction and he or she wants refractive correction, I do a clear lens exchange. I am looking forward to increased usage of the Light Adjustable Lens (RxSight; Aliso Viejo, California), the only FDA-approved IOL that can be customized through a power adjustment after it's implanted."

Dr. Wiley has also found that corneal surface procedures on hyperopes may have less refractive stability over time. "Lens replacement may be best for them," he conceded. "Hyperopia correction is trending toward lens replacement. LASIK and other corneal procedures become less viable because of the improvement that's occurred in intraocular lens technology. We once considered LASIK for patients with a correction as high as +4 D or more. As lenses keep improving, we may consider lens replacement for over +1 D. Any presbyopic patient with moderate to high hyperopia would fall into this category."



Majid Moshirfar, MD

The Kamra intracorneal inlay is placed in a femtosecond-created pocket in the non-dominant eye in order to improve a patient's near vision.

## More SMILES for Older Patients

Dr. Wiley has started using the SMILE procedure more frequently for patients over 50.

"The naturally occurring cross-linking of the corneal tissue makes the cornea strong, which helps these patients," he notes. "SMILE is less invasive, doesn't sever the corneal nerves, and minimizes dry eye, which is especially advantageous for patients over 50. Some of LASIK's biomechanical characteristics are better tolerated by younger patients. With SMILE, removal of the lenticule-shaped disc of tissue is less traumatic for the older patient. I use SMILE on patients over 50 who are between -2 and -8 D and have 3 D of astigmatism or less and a manifest refraction spherical equivalent of -8.25 D."

## Clear Lens Exchange

Like Dr. Wiley, many surgeons are correcting refractive error inside the eye more because of advanced lens technology such as the Symfony and the AcrySof. Dr. Hardten favors the Tecnis multifocal IOLs for +2.75 D, +3.25 D or +4 D. "Depending on the patient's desired second near point of focus, all of these lenses can be good options," he says.

"For an older patient who is a good candidate for surgery, I consider lens replacement to address lack of accommodation, especially in the hyperopic patient," Dr. Hardten says.

For lens replacement, Dr. Wiley also uses the Tecnis lenses and is impressed by Alcon's new Activefocus optical design for the AcrySof IQ ReSTOR multifocal IOL.

"The low add power lenses don't create the side effects of the higher add lenses of the past," says Dr. Wiley, "Patients experience less glare, fewer halos, and not as much loss of contrast and visual quality. The more near vision you provide the patient, however, the higher the side effect profile will be."

He addresses these issues by varying the lens powers. "The patient might say, 'my near vision isn't quite what I want,'" says Dr. Wiley. "Night driving might create adverse effects. So we will address that issue with less near power to reduce side effects. I will do one lens, let them drive for one to three weeks, then have them return and put in the correct lens for the other eye, with a power suited more for far or for near, depending on the patients' visual experiences."

## Offer the Best

Whether you're doing a procedure inside the eye or on the cornea, Dr. Wiley and other surgeons emphasize the need to be more flexible with the over-50 population, since it continues to grow. "We will have more patients and more options to offer them," he notes. "It puts our diagnostic skills to the test and keeps us on our toes with all of the new technology. Overall, it creates a time of great excitement and opportunity for these patients and surgeons." REVIEW

*Dr. Aker is a speaker for Johnson & Johnson Vision and Bausch & Lomb. He also serves as Medical Monitor for the CORD Group. Dr. Wiley consults for CorneaGen, J&J Vision, Alcon and Zeiss, and receives research compensation from RxSight. Drs. Hardten and Waring report no relevant financial interests.*

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# Tips for Treating Ocular Trauma

*Michelle Stephenson, Contributing Editor*

Generally, the type of injury—globe laceration vs. blunt trauma—will dictate the outcome.

Though conditions like age-related macular degeneration and glaucoma are scourges upon patients and doctors, nothing robs patients of vision as suddenly or shockingly as ocular trauma. To make matters worse, trauma cases often have to be evaluated under duress, sometimes with a tight time window in order to avoid further damage. In this article, experts outline how to deal with these cases.

## A Range of Injuries

Ocular trauma is relatively common. According to Thomas John, MD, who is in practice in Chicago, there are more than 2.4 million eye injuries in the United States annually. "Ninety percent of these are preventable, and more than 20,000 eye injuries occur in the workplace," he says.

Kevin M. Miller, MD, who is in practice in Los Angeles, says that he sees bungee cord injuries more than any other injury. "They are incredibly common," he says. "One of my patients had taken his boat out of the water and put it on a trailer. He and another person were securing a tarp over the boat, when a bungee cord came loose. The cord came flying under the boat and around to the side where he was standing. The metal hook portion went through his lower eyelid, through his eyeball, and through his upper eyelid all in one millisecond. Another guy was exercising at a gym using a bungee cord apparatus. He was sitting in the rowing position, holding the two rubber straps away from the wall apparatus, and somehow both bungee cord hooks came loose at exactly the same time. They hit him in both of his eyes simultaneously. He went from a high-functioning executive to being basically blind in both eyes."

Blunt trauma is also common. Injuries include fist injuries, racquetball injuries or just getting hit in the eye with a cabinet door or table edge.

There are also projectile injuries, such as flying glass during automobile accidents, and gunshot wounds. "A lot of people try to kill themselves by putting a gun up to the side of their temple," Dr. Miller says. "When they pull the trigger, the bullet goes through both eyes, but doesn't kill them. There are quite a variety of injuries."

He says that people who suffer ocular injuries rarely lose their sight or their eye. "In the majority of open globe injuries, people retain vision," Dr. Miller says. "It may not be the greatest vision, however. It depends on how badly damaged the retina is. They might end up going through a couple of years of reconstructing the ante-



*This article has no commercial sponsorship.*

rior segment of the eye. The surgeon might have to do a corneal transplant, implant a glaucoma tube device, and/or implant an artificial iris. But, if the retina comes through okay, they can actually maintain pretty good vision."

## Assessing the Injury

The first step with any type of ocular injury is to determine the mechanism of injury, if possible. "Sometimes, the patient knows exactly what happened," says Darren Gregory, MD, who is in practice in Aurora, Colorado. "Sometimes, it's the middle of the night, the patient's drunk, and you can't get a good story. They know they were beaten up, but they don't know what they were hit with."

The next step is to evaluate the extent of the injury. A computed tomography scan can be performed very quickly in the ER. "This can show you details about what's going on in the eye," explains Uday Devgan, MD, who is in practice in Los Angeles and teaches UCLA ophthalmology residents at Olive View-UCLA Medical Center. "You can have a ruptured globe and the lids are so swollen and the [patient's eye] so tender, it's hard to examine him or her. But a CT scan will tell you if any of the orbital bones are broken. It can tell you if there's a posterior rupture. The eye is like a round ball, but if somebody hits the front of the eye really bluntly, like with a knuckle, it may blow out the back of the globe. So, you can have a posterior rupture, which can easily be seen on a CT scan. A CT scan can also show you if there is a retained intraocular foreign body."

It's important to get both an axial scan and a direct coronal scan. "Make sure the slices are thin enough. If you only get scans every 5 mm, you'll miss a lot of details. You want somewhere in the 1 to 2 mm range for the slices," Dr. Devgan says.

After the CT scans, the patient can be examined clinically. Dr. Devgan recommends first checking a patient's vision. "Then, you can examine the front of the eye and the lid to make sure there are no significant issues or lacerations there," he says. "A slit-lamp microscope can be used to look at the front of the eye. It's important to know where the eye typically ruptures and look there. For example, one of the places is where the extraocular muscles attach to the sclera. The sclera tends to be a little thinner there and can rip in those areas. If the patient has had cataract surgery, the eye can rupture at the site of the phaco incisions, even if it's 10 or more years later."

Dr. Devgan also recommends examining the iris, which has the ability to plug up a leak. "Much like when you have a stab wound or a bullet wound in your abdomen and the omentum plugs up the leak, the iris can plug up an anterior segment leak or rupture," he says. "If the eye has a rupture, the iris will be peaked and pointed toward the area of the rupture. If possible, get a view of the back of the eye. If the eye is full of blood, a B scan ultrasound can be used to look back there, as well."

Dr. Miller adds that it can often be difficult to assess a patient's ocular trauma immediately after an accident because he or she may have injuries to other parts of the body that are also being evaluated.

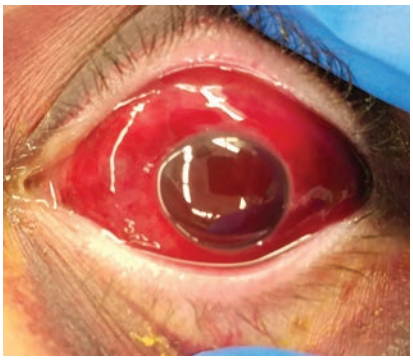

Figure 1. A massive subconjunctival hemorrhage in a 30-year-old following an assault (the amount of hemorrhaging is very suggestive of a globe rupture even though there is no visible rupture).

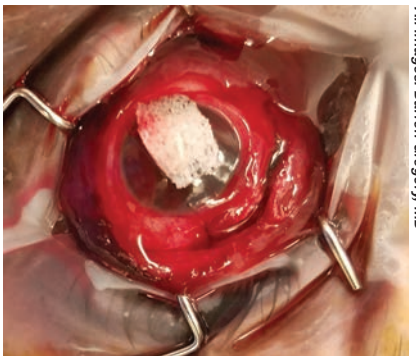

Figure 2. A large circumferential rupture of the superior sclera 3 mm posterior to the limbus in the same patient.

All images: Darren Gregory, MD

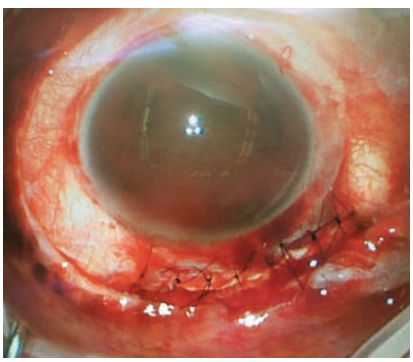

Figure 3. The suture repair of the patient's laceration.

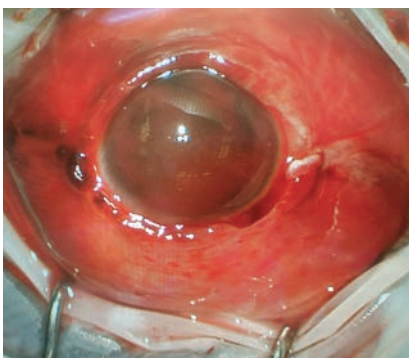

Figure 4. The same eye following closure of the conjunctiva over the scleral defect. The patient had a retinal detachment that was repaired a week later, but vision only recovered to the 20/200 range.

## An Intact Globe

Treatment can typically be delayed

if the patient has an intact globe. "It often doesn't require immediate surgery that day or night," Dr. Devgan explains. "With anterior segment trauma that's not rupturing, you'll typically see damage to the iris and lens. Posterior trauma can include damage to the retina, the choroid, and the other layers of the posterior segment, as well. Those usually can be fixed a little bit later; [the repair] doesn't have to happen right away."

## A Ruptured Globe

A ruptured globe is a severe injury. It's sight-threatening, and there is the potential that the patient could lose the eye. "Patients with ruptured globes, such as those who have been in a car crash, may also have severe head and/or brain trauma," Dr. Devgan says. "When you're called to the ER to see a patient with a ruptured globe, you must determine the extent of the trauma. Is it limited to the eye and the orbit, or does it also involve other body parts? With the brain particularly, it can be life-threatening."

Besides car accidents, ruptured globes are typically the result of assault or industrial accidents. "Then, there's the wild card: Every July 4th, we get patients with combined hand and eye injuries," Dr. Devgan says. "They light up their firework and if it doesn't work, they pick it up and look at it, and it goes off in their hand toward their face."

Ocular trauma with a ruptured globe is less frequently seen in private practice, according to Dr. Devgan. "I've been in practice 20 years, and I've seen one ruptured globe in my private subspecialty clinic," he says. "At the county hospital where we do our residency training, we see at least one ruptured globe a week. On July 4th weekend, it will probably be two or three. One year, we had six in one weekend."

When treating these patients, experts say it's important to manage patient expectations. If a patient has a ruptured globe, there is a lifetime risk of sympathetic ophthalmia. "Because of the rupture, some of the antigens that are present in the eye, which are normally never seen by the immune system, are now presented to the immune system," Dr. Devgan says. "The immune system can attack not only the bad eye, but the good eye, months or even years later. Because this is a lifetime risk once you have a ruptured globe, it has to be in the consent form for the procedure to repair the ruptured globe. It's critical for the patient to know that it's very difficult to return an eye that has suffered a ruptured globe back to normal. The goal is just to close the globe today, not to restore sight. In fact, this patient may never get useful sight back out of the eye. There's always the risk that you may lose the whole eye. We must manage expectations and paint a realistic picture before performing surgery."

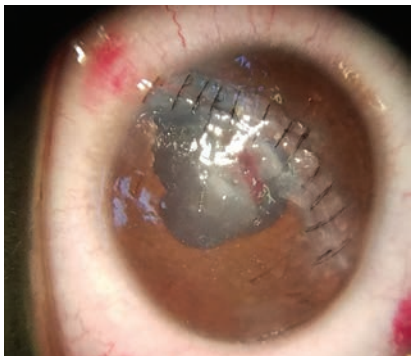

Figure 5. A 9-year-old boy who was stabbed in the eye with a pencil. The suture repair of the corneal laceration is shown. There was also violation of the lens capsule. A cataract and elevated IOP soon developed. The cataract was removed three to four weeks following the initial injury. Due to iris and zonular damage, the patient was left aphakic, but he has achieved 20/30 vision with a soft contact lens. This and the Case on p. 47 show how the visual prognosis with a globe laceration from a sharp object is generally better than with a globe rupture from blunt trauma.

Especially if it's in the middle of the night, the goal is just to close the eye. Dr. Devgan says the surgeon can come back in a few days or weeks and fix the traumatic cataract or retinal detachment. "During the initial surgery, our goal is to remove any intraocular foreign body and close the globe," he adds. "If we can fix other damage at the same time, we will, but it depends on the severity of the trauma."

## Chemical Burns

Fifteen percent of eye injuries are a result of burns. "With chemical injuries, alkali is the worst because it can penetrate the ocular structures much faster than acid," notes Dr. John. "Alkali rapidly disrupts the cell membranes and penetrates into the tissues. Acid is usually less damaging due to the binding and buffering of the acid by the corneal protein. When that happens, the coagulated tissue can act as a barrier and prevent further penetration. The most important thing is to irrigate as soon as possible."

Chemical ocular injuries can range from very mild to very serious. "In Grade 1, the injury is very superficial," Dr. John explains. "With such minor injuries, there is little ischemia, and the cornea is completely clear. With Grade 2, there is minor corneal haze and localized focal limbal ischemia. In Grade 3, there is pronounced corneal haze, and the view of the anterior chamber is compromised. There is significant ischemia of the limbus. The worst is Grade 4, where the cornea is opaque and porcelainized. It's extremely prone to melting in the acute or intermediate time frames after injury. Depending on the extent of the injury, the visual loss can be mild, or there can be total loss of vision."

## Enucleation of the Eye

Surgeons typically don't perform a primary enucleation of the eye immediately after the injury. "We usually try to let patients come to terms with the severity of their injury," says Dr.

Gregory. "If they have a blind, painful eye or a severely disfigured eye, they may choose to have it removed. However, that's usually difficult psychologically. And it's surprising how many cases that look almost hopeless end up with more vision than you initially anticipated."

He believes that it's best to close the hole as well as you can to stabilize the eye, "let the dust settle" a little bit, and monitor for signs of infection or problems with the intraocular pressure either being too high or too low. "If the eye begins to stabilize, then you can start looking at repairing the damage that's occurred inside the eye, whether it's removal of vitreous hemorrhage and repair of a retinal detachment or replacement of the lens," Dr. Gregory says. "Especially with ruptures from blunt trauma there's often prolapse of the lens out of the eye, whether it's an artificial lens or a natural lens. If it ruptures anteriorly, there's often damage to the iris and the pupil, which may require some repair at a later date, as well."

## The Million Dollar Eye

When a patient has undergone ocular trauma in one eye, it's important to turn your attention to the fellow eye. "There is the concept of the million dollar eye and the hundred dollar eye," Dr. Devgan says. "The eye that's already severely damaged is the hundred dollar eye, and the better eye is the million dollar eye. You don't want to lose a good eye, right? So, the million dollar eye should not be neglected. For example, if a patient has a ruptured globe from grinding metal, a little fragment of metal could be in the fellow eye without us knowing it. So, you have to examine what you think is the non-traumatized eye in great detail, as well."

Dr. Devgan says the number one risk factor for a ruptured globe is a previous ruptured globe, because the patient may continue to do the high-risk activities that caused the injury the first time. "Let's say you're a gardener and there are tree branches on the left side of your face, but you've lost vision in your left eye and can't see them," he says. "You turn your head, and the branches poke you in the good eye. This is why people with a ruptured globe need to be in protective glasses and have monocular precautions for the rest of their lives. If the patient feels that it looks goofy to wear safety goggles every day, we can even place polycarbonate lenses in Ray-Ban frames, so the patient will look cool while being protected."

Though dealing with an ocular injury demands a lot from the clinician and surgeon, physicians say that moving quickly—but not rushing—and taking a logical approach can often lead to the best possible outcomes. REVIEW

*None of the physicians interviewed have any financial interest to disclose.*

*(Continued from page 34)*

simulate the adjustment first to make sure I'm not doing unnecessary surgery.

"We do a fair number of those simulations," he adds.

• ***Take the age of the patient into account.*** "I would definitely perform a refractive correction on younger patients in their 40s and 50s," notes Dr. Trattler. "Those patients have very high expectations, so if we're off-target with one of these patients, we follow our process. We treat their dry eye, perform the YAG capsulotomy, then undergo a contact lens trial, and finally perform the refractive enhancement. As far as which option to use for the adjustment, younger patients are eligible for all of the options; any of them are appropriate."

Dr. Berdahl notes that—for better or worse—older patients seem more willing to accept imperfection than younger patients. "In general, I find that older patients are easier to work with than younger patients," he says. "They've had a number of procedures over the course of their lives, and not all of them have turned out perfectly. As a result, they're more willing to accept imperfection than younger patients who haven't been through multiple diagnoses and medical treatments."

## It's All Good

Surgeons note that the good thing about most instances of refractive surprise is that multiple corrective options will work, giving the surgeon some leeway.

"The good news is that all of the technologies available to us—IOL exchange, piggyback lens and laser refractive surgery—can be used in almost any refractive-surprise situation," says Dr. Trattler. "So although I have my own preferences, I wouldn't fault someone who has a different preference. If a surgeon wants to use a piggyback lens on a -2-D patient, that's OK. If you want to do PRK on a +1.5-D patient, that could also work. It's not like anything is set in stone. The bottom line is that we're using a variety of technologies and procedures to make our patients happy." REVIEW

*Dr. Trattler has consulted for VISX, Johnson & Johnson Vision, ORCA Surgical and Bausch + Lomb. Dr. Berdahl has consulted for Astigmatismfix, Alcon, Johnson & Johnson Vision, Bausch + Lomb and RxSight. Drs. Lee and Ouano report no financial ties to any product discussed.*

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2. Fernández-Buenaga R, Alió JL, Ardoy ALP, et al. Resolving refractive error after cataract surgery: IOL exchange, piggyback lens, or LASIK. J Refract Surg 2013;29:10:676-683.

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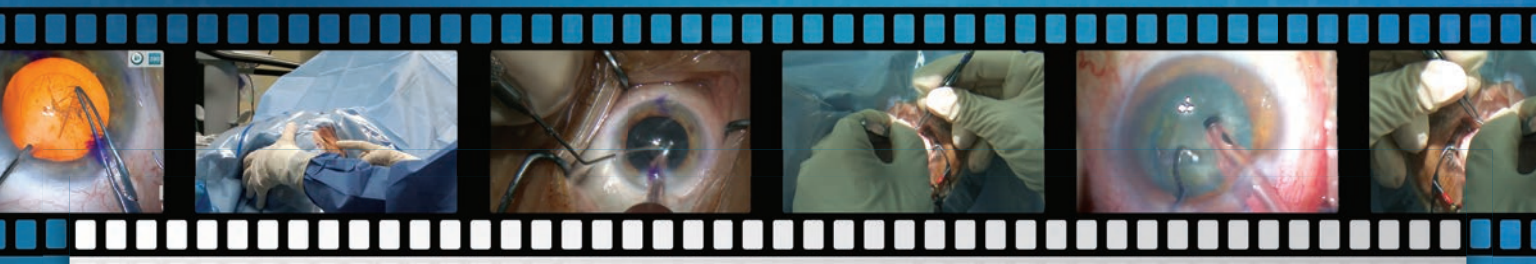

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# The Ischemic Index In CRVO Cases

**In a single-center,** retrospective cohort study of 60 treatment-naïve central retinal vein occlusion patients, researchers sought to understand the relationship between baseline ischemic index (IsI) values calculated with ultra-widefield fluorescein angiography (UWFFA) and classification as an ischemic CRVO.

Researchers identified 60 eyes of 60 patients who were diagnosed with a CRVO between 2009 and 2016. The criteria for an ischemic CRVO included having an afferent pupillary defect and counting fingers vision or worse and/or neovascularization not attributable to another disease. Logistic regression was used to evaluate the relationship between IsI and the clinical outcomes.

The study found that patients with an IsI ≥35 percent were significantly more likely to become ischemic during the first year of follow-up than those with an IsI <35 percent (83.3 versus 13.9 percent, odds ratio 111, $p<0.00001$). In eyes with an IsI ≥35 percent, baseline and final logarithm of the minimum angle of resolution (logMAR) acuity were worse than those with IsI <35 percent (1.18 [a little better than 20/400] versus 0.46 [a little worse than 20/50], $p<0.001$ and 1.26 versus 0.45, $p<0.001$).

For eyes with IsI ≥35 percent, the researchers calculated a 50-percent probability of classification as ischemic CRVO in the one-year follow-up timeframe. The researchers also found that eyes with an IsI ≥35 percent were 100 times as likely to be classified as ischemic and six times as likely to have final acuity of 20/200 or worse in the first year of follow-up compared to eyes with an IsI <35 percent. Observed differences in vision were attributed in part to a greater prevalence of ischemic maculopathy and foveal avascular zone enlargement in eyes with an IsI ≥35 percent.

*Retina 2019;39:6:1033-8.*

Thomas AS, Thomas MK, Finn AP, Fekrat S.

## Nailfold Capillary Blood Flow And Exfoliation Glaucoma

Researchers from New York, Boston and Chiang Mai, Thailand, say that, since analyzing patients' blood flow using nailfold capillaroscopy has demonstrated alterations associated with high-tension glaucoma and normal-tension glaucoma, it's possible that exfoliation glaucoma may also cause such changes. They undertook a study to try to find a connection.

The cross-sectional, clinic-based study was carried out at the New York Eye and Ear Infirmary of Mount Sinai from July 6, 2017, to May 18, 2018. The researchers studied 111 patients (30 XFG, 30 NTG, 30 HTG, and 21 controls). Exclusion criteria were the presence of connective tissue disease, uncontrolled diabetes, history of bleeding disorders, and/or history of trauma or surgery to the nondominant hand. The primary outcome was resting capillary blood flow at the nailfold of the fourth digit of the nondominant hand in patients with XFG, NTG, HTG and controls, using nailfold capillaroscopy.

Ultimately, two participants were exluded due to poor nailfold image quality, leaving 109 patients for the final analysis. Sixty-two participants (57 percent) were women and 79 (72 percent) were white. The average age of the participants was 67.9 ±11.7 years.

Mean resting peripheral capillary blood flow at the nailfold for controls was 70.9 ±52.4 picoliters/s (pL/s); HTG: 47.5 ±41.9 pL/s; NTG: 40.1 ±16.6 pL/s; and XFG: 30.6 ±20 pL/s. Multivariable analysis of the differences of flow in HTG vs control participants showed values of -18.97 (95% CI, -39.22 to 1.27; $p=0.07$) pL/s, NTG vs. controls of -25.17 (95% CI, -45.92 to -4.41; $p=0.02$) pL/s, and XFG vs. controls of -28.99 (95% CI, -51.35 to -6.63; $p=0.01$) pL/s.

The researchers say the study hints at the systemic nature of glaucoma, since the resting peripheral capillary blood flow decreased in patients with exfoliation and normal-tension glaucoma.

*JAMA Ophthalmol 2019;137:6:618-625.*

Kertes PJ, Galic IJ, Greve M, et al. FUS and the Rubella Virus-Associated Uveitis

## FUS and Rubella Virus-Associated Uveitis

Researchers in the Netherlands sought to investigate and expand knowledge of ocular manifestations and complications of RV-associated uveitis and to demonstrate its relation to rubella vaccination and Fuchs uveitis syndrome.

A retrospective study of 144 eyes of 127 uveitis patients RV-positive in aqueous humor analysis was carried out. Patients were chosen from between January 2010 and October 2016. The average age at presentation was 37, and no cystoid macular edema was encountered preoperatively. None of the patients was vaccinated against RV. Uveitis was classified mainly as anterior uveitis or panuveitis, despite vitritis in 103 (81 percent) patients.

During the study, cataracts affected 67 percent of patients and five eyes presented with glaucoma at the end of follow-up. Thirty-nine patients presented with complete FUS phenotype, with 37 testing positive for RV (95 percent) and two patients (5 percent) testing negative. No alternative cause of uveitis was found in the two RV-negative FUS patients.

The researchers conclude that RV-associated uveitis and FUS aren't exchangeable. RV-associated uveitis has a wider spectrum of clinical signs than typical features of FUS phenotype. This study supports the finding that FUS is mostly caused by RV in Europe. However, the researchers note that FUS has other causes such as CMV, *T. gondii*, and trauma, and not all RV-associated uveitis cases exhibit classical features of FUS. In this study, RV occurred in the aqueous humor of nearly all FUS patients, but RV presented as FUS only in a minority.

The researchers say that with correct diagnosis of RV-associated uveitis patients can avoid unnecessary immunosuppressive therapies and corticosteroids.

*Am J Ophthalmol 2019;202:37-46*

Groen-Hakan F, Van de Laar S, Van der Eijk-Baltissen A, Ten Dam-Van Loon N, De Boer J, Rothova A.

## Survivor: Goldmann Tonometer

Because calibration error (CE) is one of the most common sources of error for Goldmann applanation tonometers, researchers implemented a preventative maintenance program for 190 tonometers to measure survival rates and report maintenance outcomes.

The prospective cohort study was carried out at two tertiary eye care referral centers on slit-lamp-mounted GATs (Model AT 900 C/M; Haag-Streit). The maintenance program consisted of monthly testing by ophthalmologists for one year. Reported repairs were fixed within 24 hours. Only CE at the clinically significant level of 20 mmHg was reported.

Acceptable CE level was deemed ±2 mmHg at all levels of testing. Instruments were considered faulty if the CE exceeded this limit at any testing level. Failure was defined as having developed an unacceptable CE beyond the third repair. The outcome measures included frequency of CE and the survival rate of the tonometer.

Sixty-three tonometers (33.1 percent) needed more than one repair. The remaining 127 instruments (66.8 percent) required no repairs. Of the GATs requiring repair, 49 (77.7 percent) needed one repair, five (7.9 percent) needed two repairs, two (3.1 percent) required three and seven (11.1 percent) developed unacceptable CE after the third repair and were removed from the program.

Among tonometers requiring one CE repair, the survival rate was 100 percent. For those requiring more than one repair, the survival rate was 0.64 after three months, dropping to 0.40 at the end of the study. The maintenance program didn't halt the decline of units requiring maintenance, and the researchers reported that the number of repairs rather than the age of the unit determined survival. The researchers concluded that these monthly maintenance procedures can save time and money.

*J Glaucoma 2019;28:6:507-11*

Choudhari NS, Richhariya A, Wadke V, Deshmukh SP, George R, Senthil S, Sekhar GC.

## Restrictive Strabismus After Pterygium Excision

Researchers from San Diego and the Tel Aviv, Israel, conducted a study to report characteristics of restrictive strabismus and diplopia development in patients following pterygium excision and approaches to treating postoperative restrictive strabismus.

The retrospective interventional case series was carried out at a single academic institution on 15 patients (mean age 49) who developed restrictive diplopia after pterygium excision. Inclusion criteria for diplopia on presentation was a history of ≥1 pterygium excision procedures before presentation of diplopia. Cases of diplopia due to other reasons were excluded.

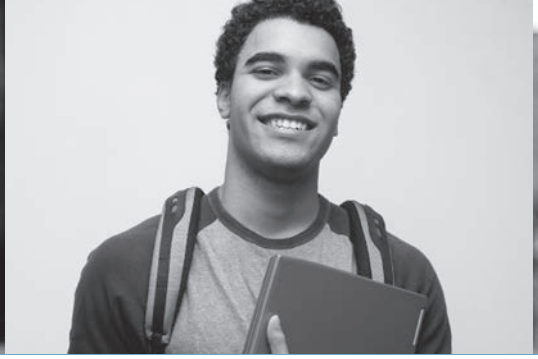
The researchers report that all patients had an esotropia after excision of pterygium, which caused the diplopia. The mean time for diplopia onset after the last surgery was six months.

A combined procedure to remove scar tissue formation and improve diplopia was performed by a strabismologist and an oculoplastic surgeon. Amniotic membrane grafts secured with sutures rather than fibrin glue were used on all 15 patients. At 24 months of follow-up, only two patients required surgical intervention, which led the researchers to believe that securing AMGs with sutures was less inflammatory than glue, though no direct comparison was done.

Given the frequency of pterygium excision and AMG placement with glue, the researchers say that it's important to be aware of the possibility of postoperative restrictive strabismus and its correction potential. REVIEW

*Am J Ophthalmol 2019;202:6-14*

Baxter S, Nguyen B, Kinori M, Kikkawa D, Robbins SL, Granet DB.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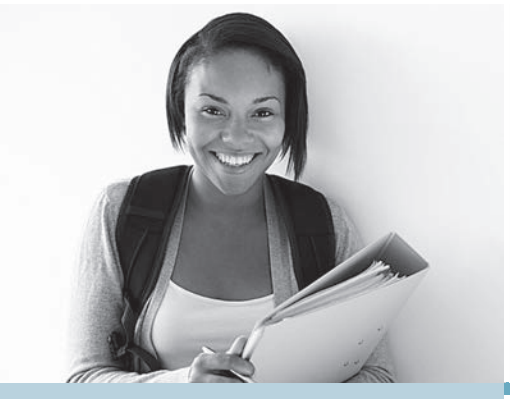

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# Clinical Pearls for a New Condition

Pentosan polysulfate therapy, a common treatment for interstitial cystitis, has been associated with a maculopathy.

*Adam M. Hanif, MD, and Nieraj Jain, MD,*
*Atlanta*

**Modern imaging and** the relative ease of genetic testing have enabled ophthalmologists to take great strides forward. As these advancements heighten diagnostic precision, physicians are becoming better equipped to detect novel pathology. We recently identified a unique pigmentary maculopathy in a cohort of patients who were receiving chronic pentosan polysulfate sodium therapy (Elmiron, Janssen Pharmaceuticals, Titusville, New Jersey), a popular medication for interstitial cystitis.[1] Upon presentation to our clinic, these patients carried tentative diagnoses, including age-related macular degeneration and pattern dystrophy. Our subsequent investigations of this novel phenotype are suggestive of a preventable, vision-threatening medication toxicity that could masquerade as other known maculopathies. Here, we offer a clinician's primer on what is known about this condition and how to avoid missing it in the at-risk patient.

## Background

Interstitial cystitis is a chronic regional pain syndrome of the bladder and pelvis that predominately affects females, manifesting with urinary urgency and dyspareunia.[2] More than 1 million people in the United States are estimated to be affected by this condition, which can also disrupt sleep and lead to emotional stress.[3] There are only two FDA-approved therapies for IC: intravesical dimethyl sulfoxide and oral pentosan polysulfate sodium.[4] PPS is a semi-synthetic analogue of biologic glycosaminoglycans, thought to act by binding to the bladder's epithelial lining, regulating irritation and cellular permeability.[5-9] Although it has been widely prescribed for decades, no known ocular toxicity had previously been reported.[10]

In a 2018 report, we described unique macular pigment changes observed in six patients receiving chronic therapy for IC with oral PPS.[1] Patients primarily identified symptoms of blurry vision and prolonged dark adaptation. On dilated fundus exam, these patients exhibited subtle macular pigmentary changes, yet fundus autofluorescence and near infrared reflectance imaging of the posterior pole revealed a striking pattern of abnormalities.

Despite a thorough review of medical history and comprehensive molecular testing, no known acquired or inherited etiology accounted for these findings. This series presented to us compelling evidence of a previously unrecognized medication toxicity, necessitating further investigation

**Table 1: Consolidated Clinical Observations**

| | |
|---|---|
| **Median Age:** | 60 years (range: 37 to 79 years) |
| **Median Duration of PPS Intake:** | 14.5 years (range: 3 to 22 years) |
| **Common Presenting Symptoms:** | Blurred vision while reading (48.6 percent)<br>Prolonged dark adaptation (48.6 percent)<br>Metamorphopsia (11.4 percent) |
| **Median Duration of Visual Symptoms:** | 4 years (range: 1 to 9 years) |
| **Median Visual Acuity:** | OU: 20/25<br>OD Range: 20/20 to 20/300<br>OS Range: 20/15 to 20/400 |

Data documented in a series of 35 confirmed cases of PPS-associated maculopathy.[12]


*This article has no commercial sponsorship.*

of causality and phenotype.

## Investigation of Causality

Our subsequent investigations demonstrated that this unique maculopathy is strongly associated with chronic PPS exposure, not IC itself or its other therapies. In fact, this characteristic maculopathy has, to date, been exclusively diagnosed in patients reporting prior PPS exposure. To draw this conclusion, we conducted a retrospective, cross-sectional study at our institution to evaluate risk factors for development of the maculopathy.[11] All patients of the Emory Eye Center who had been diagnosed with IC within a four-year period were included in the study.

The medical charts and pharmacy records of these patients were reviewed for documentation of exposure to IC therapies, including PPS, hydroxyzine, tricyclic antidepressants, gabapentin, pregabalin, cyclobenzaprine, methenamine, phenazopyridine and oxybutynin. Histories of hydroxychloroquine use and cigarette smoking were also included. Finally, expert reviewers masked to medication history reviewed ophthalmic images of all patients to identify cases of this unique maculopathy.

Of the 219 IC patients included in the study, 80 (36.5 percent) had prior documentation of exposure to PPS. Masked reviewers identified 14 cases of the characteristic maculopathy, each occurring among the 80 PPS-exposed patients.

No patient exhibited this maculopathy in the absence of PPS exposure. Among all potential risk factors examined, PPS exposure emerged as the sole statistically significant predictor of this maculopathy ($p<0.0001$). Median duration of PPS intake among affected patients was 18.3 years (range: 3 to 21.9 years). The cumulative medication exposure for this grouping of patients was 2.3 kg (range: 0.58 to 2.98 kg) across this timespan.

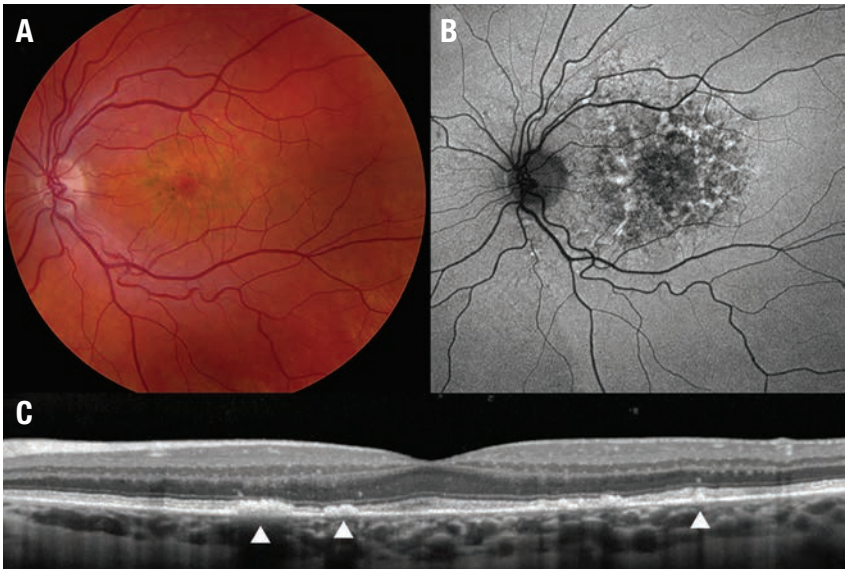


Figure 1: Representative images of a patient with PPS-associated maculopathy. A. Color fundus photography reveals paracentral hyperpigmented spots and yellowish subretinal deposits. The hyperpigmented spots appear to be an early manifestation of the condition; they are often absent in late, atrophic disease. B. Fundus autofluorescence imaging reveals striking AF abnormality, with a fairly well-circumscribed, central patch of hyper- and hypoautofluorescent spots. C. Optical coherence tomography imaging reveals focal nodules of hyperreflectance at the level of the RPE, found to co-localize with hyperpigmented spots.

## Population at Risk

As the only FDA-approved oral agent for IC, PPS has been a mainstay of treatment for decades. Using claims data from a national U.S. insurer, we identified practice patterns suggesting hundreds of thousands of individuals have likely been exposed to the drug within the United States.

In a retrospective, matched cohort study within this large database, PPS-exposed patients were found to have a significantly increased risk of being diagnosed with a new macular disease at seven years.[12]

This study also suggested that chronicity of exposure plays a role; at the five-year timepoint of continuous treatment, there was a trend for increased risk, although it wasn't statistically significant.

## Clinical Features

The largest case series to date analyzed 35 patients with a confirmed diagnosis of PPS-associated maculopathy across four institutions, where the median age at the time of diagnosis was 60 years (range: 37 to 79 years) (*Table 1*).[13] The median PPS intake duration was 14.5 years (range: 3 to 22 years), at a median daily dose of 300 mg (range: 150 mg to 592 mg), consistent with recommended therapeutic regimens.[9] Median cumulative intake per kilogram of body mass was 24.7 g/kg (range: 9.83 to 61.9 g/kg).

Of note: Given the recent recognition of this entity, this series likely represents a group of patients with relatively advanced disease, and it doesn't fully capture the exposure characteristics and clinical findings of those with incipient disease.

Patients most commonly had a referral diagnosis of macular or pattern dystrophy (45.7 percent) and/or

AMD (28.6 percent), and reported symptoms, including blurred vision while reading (48.6 percent), prolonged dark adaptation (48.6 percent) and metamorphopsia (11.4 percent). The median visual symptom duration was reportedly four years (range: 1 to 9 years). Visual acuity was relatively well-preserved, with median logarithm of the minimum angle of resolution (logMAR) values from both eyes measured to be 0.10 (Snellen equivalent, 20/25; OD range: 0 to 1.18, OS range: -0.12 to 1.30, $p$=0.93). Only 10 eyes (14.3 percent) had visual acuities lower than 20/40, of which two (2.9 percent) had visual acuities lower than 20/200. Humphrey visual field testing was typically fairly normal except in the setting of patchy atrophy of the retinal pigment epithelium.

On examination, patients often had paracentral spots of hyperpigmentation accompanied by pale yellow or orange deposits (*Figure 1A; Table 2*). Generally, these spots initially appear in the parafoveal region and extend peripherally within the macula over time, indicating a dynamic disease process.

RPE atrophy exceeding one-third of a disc diameter was observed in 39.4 percent of cases, involving the central fovea in 9.1 percent. Spots of hyperpigmentation occurred less often in eyes with atrophy (23.1 percent) than in those without atrophy (73.7 percent, $p$<0.00007).

FAF (*Figure 1B*) imaging reveals the full extent of the fundus abnormality, which typically centers on and involves the fovea. Pathology is often characterized by a fairly well-circumscribed patch of affected retina involving the posterior pole, as was seen in 56.1 percent of patients.

However, in some cases, the FAF abnormality exhibits a more diffuse pattern, extending into the retinal periphery. Characteristic patterns within these lesions resembled densely packed hyper- and hypoautofluorescent spots and reticular hyperautofluorescent changes.

**Table 2: Documented Imaging Findings**

| |
|---|
| **Color Fundus Photography** |
| Bilateral, symmetric pathology* |
| Centered on and involving the fovea* |
| Spots of hyperpigmentation (50 percent) |
| **Fundus Autofluorescence** |
| Dense pattern of hyper-/hypoautofluorescent spots* |
| Well-circumscribed region of disease (>55 percent) |
| RPE atrophy exceeding 1/3 disc diameter in size (40 percent) |
| Center-involving atrophy (9 percent) |
| **Optical Coherence Tomography** |
| Discrete lesions of RPE thickening* |
| Ill-defined irregularity in outer retinal bands* |

* Observed in all affected eyes

Summary of imaging findings organized by modality, documented in a recent series of 35 confirmed cases of PPS-associated maculopathy (manuscript under review).

OCT imaging (*Figure 1C*) reveals nodular thickening of the RPE that also co-localizes to the spots of hyperpigmentation observed on color fundus photography and as hyperreflectance on NIR imaging. The yellow or orange deposits observed on color fundus photography lack a clear anatomic correlate on OCT imaging, although similarly localized disruptions in the outer retinal bands may suggest that the deposits occupy the subretinal space.

All affected eyes in the cases contain regions with abnormality in the interdigitation zone, or a confluence between the interdigitation zone and ellipsoid zone bands.

Cystoid macular edema was observed in nine eyes of six patients. These cases responded well to treatments, including topical dorzolamide, and intravitreal afibercept and bevacizumab. One eye in the series developed subretinal exudation attributed to choroidal neovascularization.

## Discussion

These findings bolster growing concern about a newly described medication toxicity and raise significant public health implications. Thousands of unscreened patients may be at risk. Importantly, many of these cases may have masqueraded for years as similar-appearing conditions, such as AMD and pattern dystrophy. A unique pigmentary maculopathy is strongly associated with chronic exposure to the IC drug PPS. The fundus findings in PPS-associated maculopathy are subtle, yet exhibit a distinctive clinical phenotype on multimodal imaging that's best appreciated by using FAF. Preliminary investigations of databases indicate that many thousands of patients may be at risk.

Several possible explanations exist for this condition's recent discovery, relative to the FDA approval of PPS in 1996.[14] First, chronic exposure generally seems a prerequisite for this condition. We may only now be seeing the subset of patients who have exceeded the exposure threshold at which this disease begins to manifest. Secondly, IC patients can be complex, harboring conditions that affect multiple organ systems treated with numerous medications. This can make identifying a drug-disease association difficult.

The presenting visual symptoms for these patients are vague, and retinal changes on conventional examination are subtle. Modern retinal imaging modalities, including AF, recently adopted widely, can help detect changes. Without referral to a specialist with modern imaging instrumentation, PPS-associated maculopathy may remain undetected. Many existing cases may masquerade as similar-appearing conditions. Many patients with confirmed PPS-associated maculopathy are initially diagnosed with AMD and macular or pattern dystrophies. They may never pursue comprehensive retinal diagnostics, halting the diagnostic odyssey.[15]

An underlying mechanism for this condition hasn't been fully elucidated. Fundus imaging suggests a primary insult to the RPE or RPE-photoreceptor interface. Similar to processes observed in other macular dystrophies, the RPE lesions revealed by OCT may represent dying RPE cells that have accumulated pathologic levels of byproducts from the visual cycle caused by an unknown, harmful interaction with PPS. The structural homology between PPS and interphotoreceptor matrix components may permit such an interaction. The interphotoreceptor matrix, an extracellular scaffolding that mediates the photoreceptor-RPE relationship, is composed primarily of glycosaminoglycans.[16-18] PPS, a glycosaminoglycan analogue, may somehow accumulate and disrupt the structure and function of this matrix. The nodular RPE excrescences may indicate accumulation of PPS or one of its many metabolites in the RPE, as has been observed in the bladder's urothelium.[19] When radiolabeled PPS has been used to study its distribution, it has been primarily reported to deposit in the urothelium and minimally in other visceral organs.[9]

## Recommendations

Although official recommendations for evaluating at-risk patients are premature, our institution recommends discusing the lowest necessary dose and duration of treatment with long-term PPS therapy prescribers. We suggest a baseline examination with comprehensive fundus imaging (color fundus photography, FAF imaging and OCT), followed by annual examinations with fundus imaging, starting at five years after initiation of therapy. FAF imaging is valuable for highlighting the characteristic early features of the condition.

We recommend that providers exercise caution in prescribing PPS for patients with comorbid macular disease, such as AMD, which may confer a higher susceptibility to a toxic maculopathy. Patients with elevated risk, including those with an atypical dosing regimen, those with a history of smoking or macular disease and those with comorbidities involving renal, hepatic or splenic function, may benefit from more frequent examinations.

For patients with PPS-associated maculopathy, we recommend coordination with the patient and with the prescribing physician to find an alternative regimen for IC management. Although we don't fully understand the natural history of this condition, we advise affected patients that visual symptoms may persist and possibly worsen, even after drug cessation.

We expect to draw more conclusions about the incidence and history of CP. Investigations by our group and others will examine this unique phenotype longitudinally across multiple functional testing and imaging modalities to provide guidance regarding long-term prognosis. Ongoing animal studies will explore underlying mechanisms.

Given the emerging evidence linking PPS to macular disease, ophthalmologists have a new role in protecting patients at risk for this vision-threatening condition. Many of us may unknowingly follow affected patients. Many patients harboring this condition may either be undetected or misdiagnosed with similar-appearing conditions.

As in cases involving hydroxychloroquine and other drug-associated maculopathies, the use of modern fundus imaging techniques will help identify affected patients. We look forward to ongoing research developments that will improve our understanding of the pathobiology and prognosis of this unique maculopathy. REVIEW

*Dr. Hanif is a recent graduate of Emory University School of Medicine in Atlanta. Dr. Jain practices as an assistant professor in the Division of Vitreoretinal Surgery and Disease at the Emory Eye Center.*

*Please direct correspondence to Nieraj Jain, MD, 1365B Clifton Road, N.E., Suite 2400, Atlanta, GA 30322.*

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# Cross-linking in Pediatric Patients

Early intervention is key to preventing progression and the need for corneal transplantation.

*Benjamin B. Bert, MD, FACS*
*Los Angeles*

**Though corneal collagen** cross-linking has the potential to help many patients with keratoconus, the patients likely to benefit from it the most—children—may not receive it, for a variety of reasons. Here, I'll review what we know about cross-linking in patients under the age of 14, and look at ways the procedure might be able to help them.

## The Disease

Keratoconus is a progressive corneal ectatic disease that thins the cornea and creates irregular astigmatism. In advanced stages, the disease can also cause a reduction in the patient's best-corrected visual acuity.

Keratoconus remains fairly rare. Its prevalence varies in different parts of the world and by the criteria used to diagnose the condition. In the United States the rate of keratoconus has been reported as 54.5 per 100,000 in Minnesota,[1] but can range anywhere from between 4 to 600 per 100,000 depending on the diagnostic criteria used.[2]

Keratoconus management underwent a paradigm shift in the United States with FDA approval in the spring of 2016 of the Avedro KXL system and Photrexa riboflavin solutions for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.[3] This approval means that it's possible to administer the treatment right when ectasia begins, which has been hypothesized to occur around the time of puberty. If it can be stopped at that point, that would prevent 21.6 percent of patients from progressing to the need for corneal transplantation.[4] The challenge is that the original FDA studies performed by Avedro didn't include any patients under the age of 14. So, without safety data for the pediatric population, the indication ultimately approved by the FDA was for patients 14 or older.[5,6] This is of course well after most children have entered puberty, since age 13 for girls and 14 for boys is considered delayed puberty.[7]

## Diagnosis

The diagnosis of keratoconus is becoming more specific and more sensitive as our ability to image the cornea improves. Initially, diagnostic criteria were based on corneal steepness on keratometry and the scissoring reflex seen on retinoscopy. In more advanced cases, the ectactic portion of the cornea—the cone itself—could be visualized at the slit lamp.

Other findings of keratoconus that can be seen at the slit lamp include:

1) Vogt's striae: fine folds in Descemet's membrane at the apex of the cone that flatten with gentle pressure on the globe;

2) Kayser-Fleischer ring: iron deposition into the corneal subepithelial layer at the base of the cone;

3) corneal hydrops: a rupture of Descemet's membrane, leading to corneal edema and decreased vision; and

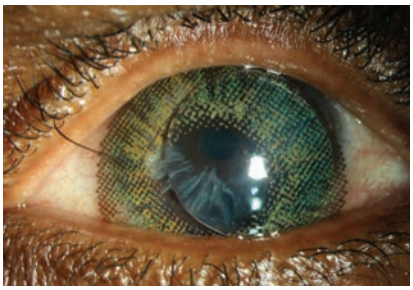
4) apical scarring: this occurs as the cone becomes steeper, or after an episode of corneal hydrops.

Everyone agrees on the diagnosis of keratoconus in these late stages when there's clear clinical evidence of the disease. However, it's the early diagnosis of cases of forme fruste or subclinical ectasia that remains controversial. With the development of topography and the progression to multiple forms of tomography, our


*This article has no commercial sponsorship.*

attempts to diagnose keratoconus earlier have become more successful.

In an effort to reach a consensus, researchers surveyed corneal experts from around the world and then held a panel meeting to discuss the results of the survey. In the debates that followed, researchers and clinicians came to some conclusions regarding the diagnosis, monitoring and treatment of keratoconus and other ectatic diseases, even though the scientific evidence wasn't clear-cut.[8] Among those conclusions was the importance of posterior corneal curvature measurements; the panel defined the presence of abnormal posterior corneal elevation as a requirement for diagnosing early or subclinical keratoconus.[8] This makes corneal tomography essential for the earliest diagnosis. Currently, imaging of the posterior corneal curvature is most often performed using Scheimpflug technology or anterior segment OCT. Recently, imaging of the corneal epithelium—primarily using OCT technology—in order to create an epithelial thickness map has become an area of intense interest in the quest for another marker for early keratoconus.[9]



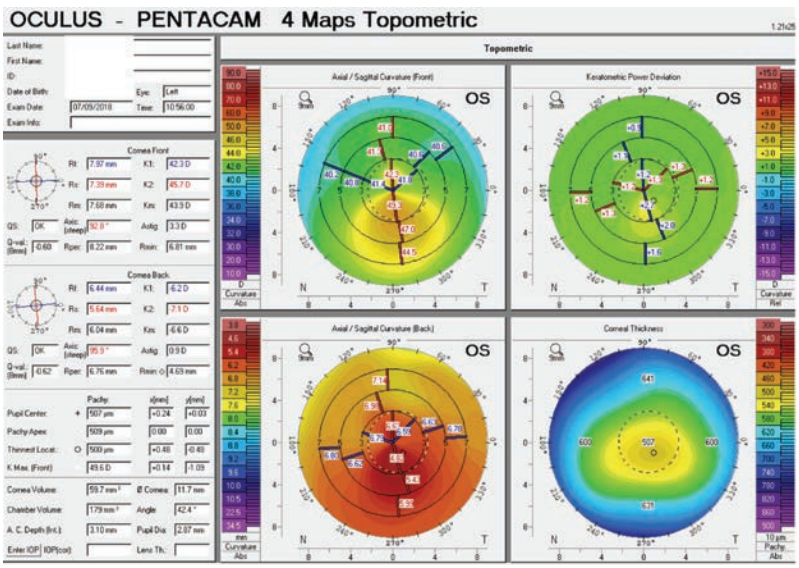
Piggyback lenses (RGP on top of cosmetic colored soft contact lens) in a patient with keratoconus.

## Treatment

The treatment of keratoconus has undergone many changes over the years, with the approval of corneal collagen cross-linking, both in the United States and abroad, being the most dramatic.

Before cross-linking, treatments for keratoconus included glasses, contact lenses (soft, hybrid, rigid gas permeable and scleral), intrastromal ring segments, full thickness penetrating keratoplasty, deep anterior lamellar keratoplasty, and the transplantation of Bowman's layer. None of these, however, adequately addressed the progressive nature of the disease. Cross-linking, with its ability to halt progression, was a paradigm shift. Since most experts agree that there's a much higher likelihood of keratoconus progression in the younger age group, the goal is to treat keratoconus at its earliest stages in the youngest ages to prevent progression, reduced best-corrected visual acuity, and the need for corneal transplantation.

Since Avedro's cross-linking system is the one that's FDA-approved, I'll be discussing it exclusively here. Currently the system is for epithelium-debrided (a.k.a., "epi-off") corneal collagen cross-linking, following what's known as the Dresden protocol. The Dresden protocol first entails removing the corneal epithelium. Then, you administer Photrexa Viscous at a rate of one drop every two minutes over a "soaking" period of 30 minutes. Next, examine the eye at the slit lamp for the presence of yellow flare in the anterior chamber. If flare is present, then you proceed with the ultraviolet treatment. If there's no flare, then you continue to administer one drop of Photrexa Viscous every two minutes for two to three more doses before checking for flare again. You then perform corneal pachymetry. If the cornea is at least 400 µm thick, you proceed to ultraviolet treatment. If it's thinner than 400 µm, you administer two drops of Photrexa (NOT Viscous) every five to 10 seconds until the pachymetric measurement is greater than 400 µm. If the cornea can't be thickened to at least 400 µm, then it's not advisable to proceed with the treatment. If you're able to proceed to the ultraviolet treatment, then apply 3 mW/cm$^2$ of energy (wavelength of 365 nm) to the cornea for 30 minutes, for a total energy of 5.4J/cm$^2$. During the 30 minutes of UV treatment, apply one drop of Photrexa Viscous every two minutes.[10]




Tomography can be useful for catching the telltale signs of keratoconus.

## Outcomes

The goal of the pilot studies was to show a reduction in the maximum keratometry measurement (Kmax) of at least 1 D. All three studies (UVX-001, UVX-002 and UVX-

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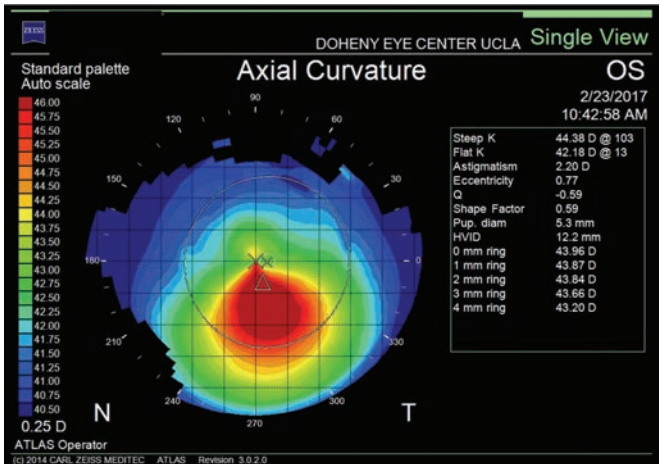
003) met this endpoint. For keratoconus specifically (included in UVX-001 and UVX-002) there was a reduction in Kmax of -1.9 D and -2.3 D, respectively, at 12 months postop.

Looking specifically at the pediatric population, a group of international researchers studied keratoconic patients ranging from 10 to 17 years old.[11] They performed the standard Dresden protocol treatment on them, and then followed them for an average of 7.5 years. During that time, though the keratometry measurements didn't improve, the researchers did note stability of the keratoconus.



The classic sign of inferior steepening on topography in a patient suffering from keratoconus.

The long-term effect of cross-linking can be seen in the trends observed internationally where cross-linking has been available for over a decade. There are a number of studies that show the rates of corneal transplants (PKP and DALK) for keratoconus decreasing after the introduction of cross-linking, intracorneal ring segments and advanced contact lens technologies. In a study from Italy's Corneal Transplant Epidemiological Study, there was a 27-percent reduction in corneal grafting for keratoconus from 2002 to 2008.[12] Much of the decline started after 2004 when cross-linking was becoming more common in Europe.

The complications that arise from crosslinking are usually related to the removal of the corneal epithelium; they include delayed healing, corneal haze, scarring and infection. In one study of cross-linking complications, researchers studied 117 eyes of 99 patients. The percentage of eyes losing two or more Snellen lines was 2.9 percent. The failure rate of CXL (which they defined as the percentage of eyes with continued progression) was 7.6 percent. They determined that a high preoperative maximum keratometry reading was a significant risk factor for failure. Sterile infiltrates were seen in 7.6 percent of eyes and central stromal scars in 2.8 percent. The researchers found that patient age older than 35 years and preoperative corrected distance vision better than 20/25 were significant risk factors for complications.[13]

## Reimbursement Issues

The biggest challenge with corneal collagen cross-linking in the United States currently is the reimbursement model. Initially, cross-linking was done as a cash-pay procedure, but since FDA approval, more insurance carriers have begun to cover it. I participated in a telephone conference with the Avedro team to discuss my experiences with the UCLA model as well as the steps Avedro has taken to help facilitate this shift.

Avedro reported that in the second half of 2018, coverage increased to 62 health insurance plans. That coverage now includes 190 million patients, or more than 90 percent of U.S. covered lives. However, billing challenges remain for both the procedure and reimbursement for the riboflavin solutions. Previously, Photrexa and Photrexa Viscous had a miscellaneous J code. Recently, CMS issued a permanent J code, J2787, effective January 1, 2019, which will help to streamline the process and avoid the erroneous rejections that can occur with a manual review. Billing errors can also arise from the procedure code being a category 3 code rather than the normal category 1 code. The process of securing the CPT code is going to take longer to finalize and may be years away. The procedure is also not reimbursed when used on patients under the approved minimum age of 14.

Since it's a new procedure, and many insurers are requiring manual reviews, a lot of rejections have resulted from an insurer's staff not being properly informed about the status of cross-linking, which they mistakenly think of as experimental. There's been some improvement lately, however. Avedro recently created a program called ARCH in order to provide information and resources for navigating coverage problems with commercial payers and improve patient access.

In addition to the ARCH program, Avedro has hired employees to provide guidance in physicians' offices, if need be. These new positions include payor relations directors who work with the insurance companies to ensure coverage and positive reimbursement, and field reimbursement managers who are up-to-date on the current regional payor landscape. The latter can work with a physician's back office and billing staff to ensure proper coding and submission, so reimbursements are processed correctly.

There will certainly continue to be hiccups along the way, but mov-

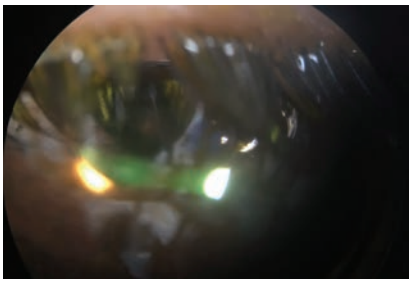
ing to an insurance payment model will make cross-linking available to a larger population, possibly including the pediatric/adolescent population who need the procedure the most, but whose parents may not be able to afford the out-of-pocket cost.

## Future Directions

To avoid complications and increase patient comfort, especially in the pediatric population, there's a lot of interest in developing an epithelium-on technique. The concern with this approach, however, is whether the riboflavin solution can achieve enough penetrance to fully saturate the cornea, and whether the UV light can penetrate adequately, as well.[14] To overcome this barrier, a couple of different techniques have been attempted, including iontophoresis[15] and disrupting the epithelium with benzalkonium chloride.[16] Studies of epi-on crosslinking have thus far shown that corneal measurements stabilize for a period of time, but then tend to progress after about a year.[17] A recent meta-analysis in the *Journal of Cataract and Refractive Surgery* concluded that for now, epi-off cross-linking should remain the standard of care.[18]

Another modification to cross-linking that would benefit the pediatric population is an accelerated protocol, so the entire procedure could be performed in much less than the hour currently required. The idea of the accelerated protocols is to deliver the same amount of total energy (5.4 J/cm$^2$) but use higher ultraviolet intensity for shorter periods of time. This means that you would need 30 mW/cm$^2$ for a three-minute treatment, 18 mW/cm$^2$ for a five-minute treatment and 9 mW/cm$^2$ for a 10-minute treatment.[19]

Some of the studies looking into accelerated protocols have also been accompanied by shorter soaking times,



Yellow/geen flare in the anterior chamber after the 30-minute "soaking" period during cross-linking.

ranging from as short as 10 minutes to the normal 30 minutes. In a review by Marcony Santhiago, MD's group, they note that many of the studies have a short follow-up period, so it's still difficult to assess the longevity of the accelerated protocol. As an indirect marker, the demarcation line has been used to signal the depth of penetrance of the treatment and a marker of successful treatment. In the standard protocol, the demarcation line is usually found around 300 to 350 µm deep. In accelerated treatments the demarcation line can be as shallow as 100 to 150 µm, which Dr. Santhiago's review found in a study of the three-minute protocol. It was only by expanding the total treatment to 14 minutes with a 9 mW/cm$^2$ treatment delivering 7.5 J/cm$^2$ that the accelerated protocols were able to deliver a demarcation line at depths comparable to the Dresden protocol.[19]

In conclusion, corneal collagen cross-linking is changing the paradigm for the treatment of keratoconus and corneal ectatic disease. It's crucial to treat patients at the youngest age at which progressive keratoconus is diagnosed, to help prevent them from needing keratoplasty or other advanced interventions in the future. REVIEW

*Dr. Bert is an assistant professor of ophthalmology at the Doheny Eye Center of UCLA, Doheny and Stein Eye Institutes, David Geffen School of Medicine.*

*He has no financial interest in Avedro's cross-linking products.*

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**Akorn says that** patients now have an affordable, convenient alternative to prescription formula eyelid cleansers with its TheraTears Sterilid Antimicrobial Eyelid Cleanser & Facial Wash. TheraTears Sterilid Antimicrobial is a 0.01% hypochlorous acid solution that comes in a 2-oz. bottle and is available over the counter. The company says the cleanser is pH-balanced to be gentle on eyelids and kills 99.9 percent of bacteria within 30 seconds.

The cleanser is intended to be a cost-effective and accessible option for patients to add to their eye hygiene regimen, the company says. While most eye-care professionals strongly recommend eyelid cleansing, only a fraction of patients suffering from dry eye regularly clean their eyelids, Akorn notes, citing Gallup market research studies. The company hopes that TheraTears Sterilid Antimicrobial will shrink this compliance gap. For more information, visit akorn.com.

## Quantel Medical's LacryStim IPL System Gains CE Approval

Quantel Medical recently announced its new CE-approved LacryStim IPL system for the treatment of dry-eye disease. LacryStim IPL is a treatment device that stimulates the lacrimal and meibomian glands and reduces inflammation by emitting a series of rapid polychromatic light pulses, the company says. The company adds that LacryStim IPL improves tear-film quality and reduces major symptoms associated with mild to moderate dry eye.


The company says this new device forms a complete diagnostic and treatment solution when paired with LacryDiag, Quantel Medical's dry eye diagnostic platform that launched in 2018. For more information, visit quantel-medical.com.

## Vera180 Synthetic Absorbable Lacrimal Plugs

To combat post-surgical dry eye, Lacrivera has released the Vera180 Synthetic Absorbable Lacrimal Plugs, designed to provide temporary occlusion lasting approximately 180 days. The company says the plugs are also ideal for treating the dry eye that accompanies various ocular surface diseases, including contact lens intolerance.

The Vera180 plugs are made of poly-p-dioxanone (PDO) and come in sizes of 0.2 mm, 0.3 mm, 0.4 mm and 0.5 mm, packaged as single pairs and in boxes of 10 pairs. For more information, visit lacrivera.com.

## Eschenbach Gives Patients a Closer Look

Eschenbach says its new desktop video magnifier, the Vario Digital Full High Definition, delivers outstanding image quality with a simple user interface and a compact folding design. For the visually impaired, the Vario Digital FHD offers a 15.6" full HD monitor with optical digital zoom from 1.3x to 45x magnification and a tilting FHD camera that provides a true color image with a large field of view.

This desktop magnifier also features LED illumination for shadow-free viewing, tactile buttons for easy operation, and a five-language voice output in menu mode. Digital storage is available through a removable 8 GB SD card and the built-in type C USB port.

The company adds that an optional, adjustable-height Video Magnifier Table with lockable wheels is also available to display the Vario Digital FHD in waiting rooms to generate patient interest. For more information, visit eschenbach.com.

*This article has no commercial sponsorship.*

## Career Opportunities


# A 72-year-old woman presents to Wills Eye Hospital with blurred central vision, floaters and a blue light in her right eye.

*Joseph A. Anaya, MD, MBA, James P. Dunn, MD, and Adam DeBusk, DO*

## Presentation

A 72-year-old woman presented with a three-day history of blurred central vision, floaters consisting of "sprinkling lights" and a blue light in the superotemporal visual field of her right eye. She didn't have any pain. Her left eye was asymptomatic.

## Medical History

Her past ocular history was notable only for myopia. Past medical history was remarkable for a right bundle branch block, lumpectomy for fibrocystic breast disease (right 2009, left 2006), hysterectomy (2008) and Bell's palsy (2005, laterality unspecified). Social history was significant for occasional alcohol consumption, but she denied any history of tobacco or drug use. Family history was notable for breast cancer in her mother and thromboangiitis obliterans and Raynaud's disease in her grandfather.

Her medications included low-dose aspirin, atorvastatin, risedronate, estradiol, mometasone nasal spray and fexofenadine. There had been no recent changes to her medications.

## Examination

Her exam demonstrated best-corrected visual acuities of 20/40 OD and 20/20 OS. Pupils, intraocular pressures and motility were normal. Color vision was 11/11 OU but slower OD. Confrontation visual fields demonstrated superotemporal constriction OD. She reported metamorphopsia on Amsler grid testing, OD only. Anterior segment examination was notable for 2+ nuclear sclerosis in both eyes. Dilated fundus examination revealed bilateral posterior vitreous detachment and peripapillary myopic degeneration; the macula was normal OU *(Figure 1 A, B)*.

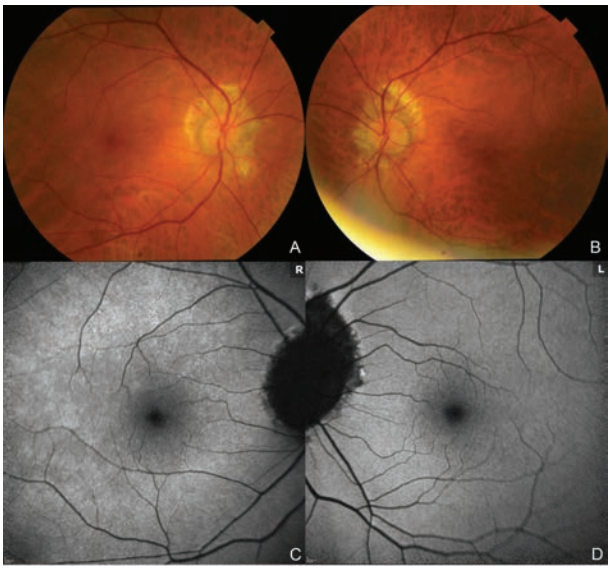


Figure 1. Fundus photos of the right (A) and left (B) eyes demonstrate peripapillary atrophy, but a normal macula in both eyes. Fundus autofluorescence images (C,D) show a mild salt-and-pepper appearance of the macula in the right eye.

***What is your diagnosis? What further workup would you pursue?*** ***The diagnosis appears on p. 64.***

## Workup, Diagnosis and Treatment

OCT demonstrated mild thinning of the macula in both eyes, with possible abnormalities of the ellipsoid zone in the right eye *(Figure 2 A,B)*. Fluorescein angiography was within normal limits. Fundus autofluorescence demonstrated a mild salt-and-pepper appearance in the right eye *(Figure 1 C,D)*. Humphrey perimetry of her right eye demonstrated superotemporal constriction, almost in the form of a superotemporal arcuate scotoma, denser temporally, as well as an inferior arcuate scotoma. This was reproduced with Goldmann perimetry *(Figure 3 A,B)*.

At this point, the differential diagnoses included the spectrum of acute zonal occult outer retinopathies, autoimmune retinopathy, and, less likely, cancer-associated retinopathy. Given the patient's severe subjective visual field worsening over a period of days, she was admitted for intravenous methylprednisolone 250 mg every six hours and further work-up. Full-field ERG demonstrated cone dysfunction in the right eye, but was normal in the left eye. Visual evoked potential demonstrated a delay in the right eye but was normal in the left. An MRI of the brain and orbits, with and without gadolinium, was unremarkable. A computed tomography scan of the chest, abdomen and pelvis showed a benign right lung nodule and small benign-appearing hepatic cysts, but no evidence of malignancy. C-reactive protein, erythrocyte sedimentation rate and complete blood count were normal. An autoimmune retinopathy panel was sent to the Casey Eye Institute and was pending at the time of discharge. She was discharged after 12 doses of IV steroids with an oral prednisone taper (60 – 40 – 30 – 20 – 10 mg daily, tapered every three days).

Two weeks after discharge, the patient's symptoms and Goldmann visual field improved dramatically *(Figure 3 C,D)*. Four weeks after initial presentation, the autoimmune retinopathy panel arrived, showing positivity for several anti-retinal autoantibodies, including HSP27, aldose, enolase, arrestin and glyceraldehyde 3-phosphate dehydrogenase. Recoverin, PKM2, tubulin and carbonic anhydrase II autoantibodies were absent. Based on the above findings, the patient's presentation was consistent with non-paraneoplastic autoimmune retinopathy.

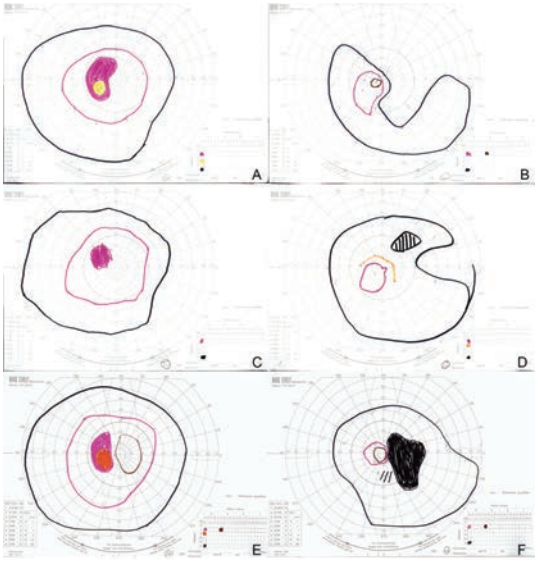


Figure 3. Goldmann perimetry at initial presentation (A,B) showed a superotemporal arcuate scotoma in the right eye. Repeat Goldmann perimetry (C,D) two weeks after receiving intravenous steroids followed by an oral steroid taper showed a dramatic improvement in the defect. Ten weeks after initial presentation (E,F) the superotemporal defect had worsened in the right eye with progression towards the central vision.

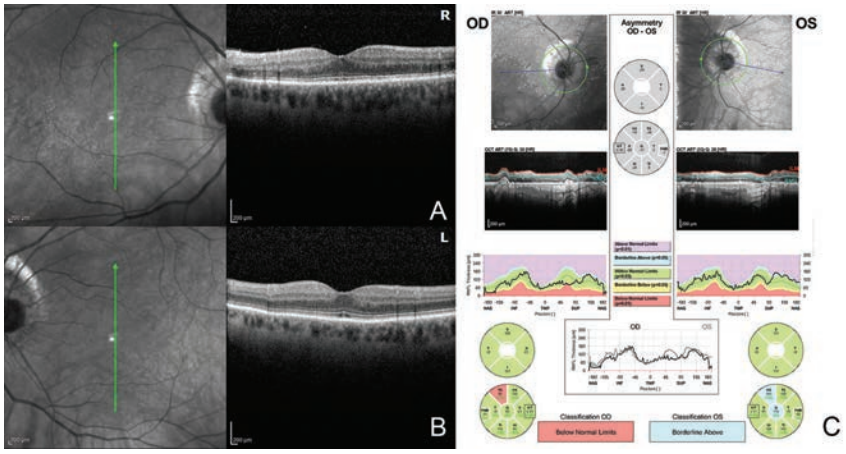


Figure 2. (A,B) OCT demonstrates mild thinning of the macula in both eyes with possible abnormalities of the ellipsoid zone in the right eye. OCT of the optic nerves (C) shows superotemporal thinning in the right eye but is otherwise normal.

She received intravitreal triamcinolone in the right eye, but denied any improvement with it. Her Goldmann visual field 10 weeks after initial presentation re-demonstrated a superotemporal scotoma in her right eye with progression toward her central vision *(Figure 3 E,F)*. Intravenous steroid therapy was reinitiated and followed with a slow oral steroid taper (methylprednisolone 1 g daily for three doses, then 60 – 40 – 20 – 10 mg daily, tapered every two weeks; then 10 mg every other day). This was administered in conjunction with starting mycophenolate mofetil 1,000 mg b.i.d. Assessment of treatment response is ongoing.

## Discussion

Autoimmune retinopathy describes a diverse group of conditions with antiretinal autoantibodies implicated in the etiology. AIR is subdivided into paraneoplastic and nonparaneoplastic subtypes, depending on the presence or absence of concomitant malignancy. While universally-accepted diagnostic criteria for nonparaneoplastic AIR remain elusive, a recent expert consensus-driven effort developed several essential diagnostic criteria *(Table 1)*.[1] These include: visual function abnormality without apparent cause or malignancy; absence of inflammation; ERG abnormality with or without a visual field abnormality; and the presence of serum antiretinal antibodies.

The differential diagnosis of nonparaneoplastic AIR includes drug toxicity, vitamin deficiencies, occult posterior uveitis, acute zonal occult outer retinopathy, inherited retinal degenerations and carcinoma- or melanoma-associated retinopathy. While drug toxicity and vitamin deficiency may be excluded with history, additional testing is often employed to investigate the cause. This testing includes OCT, fluorescein angiography, fundus autofluorescence, genetic testing and malignancy evaluation in conjunction with other specialists.[1,2]

Testing for serum antiretinal antibodies remains non-standardized and commercially available on a limited basis.[1] Consequently, concordance between laboratories may be low. One study found only 64-percent concordance between two laboratories for finding the presence of any antiretinal antibodies and 36 percent for having a positive result for a specific antiretinal antibody. The potential for such disparate results may lead clinicians to send serum samples to at least two labs.[3]

Evidence supporting the treatment of AIR is based largely on observational studies.[4] One retrospective series of 30 patients treated with systemic or local immunosuppression found that 70 percent demonstrated improvement in visual acuity or a visual field deficit.[5] More recently, a majority of patients with autoimmune retinopathy treated with rituximab demonstrated stable or improved visual acuity six months after therapy initiation.[6]

Our 72 year-old patient met the essential diagnostic criteria developed by expert consensus.[1] While her clinical exam was unrevealing, ancillary studies were notable for cone dysfunction on ERG, visual field deficit on Humphrey and Goldmann perimetry, and ellipsoid zone abnormalities on OCT. The presence of serum antibodies was confirmed; however, due to a testing turnaround time of two to four weeks and evidence that a delay in treatment may portend a worse prognosis,[6] treatment with systemic steroids was initiated prior to antiretinal autoantibody confirmation. While her visual field defect improved with steroids, she relapsed while off them and is now currently being treated with steroid-sparing immunosuppression. REVIEW

**Table 1. Essential Diagnostic Criteria for Nonparaneoplastic Autoimmune Retinopathy**

| |
|---|
| No apparent cause, lesion or dystrophy that may explain visual function abnormality |
| Absence of overt intraocular inflammation |
| ERG abnormality (with or without visual field abnormality) |
| Presence of serum antiretinal antibodies |
| Absence of malignancy |

*Adapted from Fox et al., 2016.*


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## REVIEW Advertising Index


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xiidra® (lifitegrast ophthalmic solution)5%

Rx Only

**BRIEF SUMMARY:**
Consult the Full Prescribing Information for complete product information.

## INDICATIONS AND USAGE
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.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.
For more information, go to www.Xiidra.com or call 1-800-828-2088.

Patented: please see https://www.shire.com/legal-notice/product-patents
Last Modified: 01/2018 S33769

xiidra® (lifitegrast ophthalmic solution) 5%

# THERE'S NO SUBSTIITUTE

## Xiidra is the only lymphocyte function-associated antigen-1 (LFA-1) antagonist treatment for Dry Eye Disease[1,2]

Xiidra, the first in a class of LFA-1 antagonists for Dry Eye Disease, is a prescription eye drop FDA-approved to treat both signs and symptoms of the disease.[1,3]

There's no substitute.[2,4] Check out patient resources, insurance coverage, and more at **Xiidra-ECP.com**


References:

**1.** Xiidra [Prescribing Information]. Lexington, MA: Shire US. **2.** TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-649. **3.** FDA approves new medication for dry eye disease. FDA News Release. July 2016. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm. Accessed July 12, 2016. **4.** Food and Drug Administration. Electronic Orange Book. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. Accessed June 26, 2018.


### 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.**



Shire