REVIEW® of Ophthalmology
July 2020
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GIVE YOUR PATIENTS SHARPER VISION

A SMILE expert shares his techniques. P. 30
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OMIDRIA now has a unique permanent J-code (J1097)[1]

Less stress, pure success ...in your O.R. day[2]

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 data and manuscripts 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 studies, the use of OMIDRIA statistically significantly:

- **Prevents intraoperative floppy iris syndrome (IFIS)[3]**
- **Prevents iris prolapse[3]**

Compared to steroids*:

- **Reduces cystoid macular edema (CME)[4,5]**
- **Decreases breakthrough iritis[4]**
- **Reduces pain photophobia[4]**

*OMIDRIA used intraoperatively with postoperative NSAIDs (no steroids) when compared to postoperative steroids with or without NSAIDs (no OMIDRIA).

Compared to epinephrine:

- **Decreases complication rates[6]**
- **Decreases use of pupil-expanding devices (PEDs)[6-11]**
- **Enables performance of surgery and postoperative care without the use of steroids—allowing NSAID-only anti-inflammatory therapy[4,5,7]**
- **Shortens surgical times[6,7,9,10]**
- **Reduces need for opioids (i.e., fentanyl) during surgery while decreasing VAS pain scores[12]**
- **Prevents miosis during femtosecond laser-assisted surgery[11,13]**
- **Improves uncorrected visual acuity on day after surgery[6]**

VAS = visual analog scale

OMIDRIA inhibits the release of inflammation-causing prostaglandins, preventing miosis and reducing postoperative pain[14]

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, payment, policies, and procedures may vary and should be confirmed by the facility. 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. HCPCS quarterly update. CMS.gov. Available at: https://www.cms.gov/medicare/coding/hcpcsreleasecodesets/hcpcs-quarterly-update.html. Accessed August 9, 2019. **2.** Omeros survey data on file. **3.** Silverstein SM, Rana V, Stephens 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. **4.** 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. **5.** Walter K, Kauffman L, Hess J. Rate of pseudophakic cystoid macular edema using intraoperative and topical NSAIDs alone without steroids. Manuscript submitted for publication. 2019. **6.** 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. **7.** 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. **8.** 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. **9.** 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. **10.** Matossian C, Teves N. Clinical outcomes of phenylephrine/ketorolac intraocular solution versus epinephrine in cataract surgery in a real-world setting. Manuscript submitted for publication. 2018. **11.** Walter K, Delwadia N, Coben J. Continuous intracameral phenylephrine-ketorolac irrigation for miosis prevention in femtosecond laser-assisted cataract surgery: reduction in surgical time and iris manipulation. *J Cataract Refract Surg.* 2019;45(4):465-469. doi: 10.1016/j.jcrs.2018.11.004. **12.** Donnenfeld E, Shojaei R. Effect of intracameral phenylephrine and ketorolac 1.0%/0.3% on intraoperative pain and opioid use during cataract surgery. Manuscript submitted for publication. 2019. **13.** Gayton JL. Effect of early phenylephrine and ketorolac injection 1% / 0.3% (Omidria®) usage on pupil diameter in traditional and femtosecond laser assisted cataract surgery. E-poster presented at: 15th International Congress on Vision Science and Eye; August 10-11 2017; London, UK. **14.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

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REVIEW NEWS
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As Ophthalmology Practices Reopen, Pitfalls Abound

Closing ophthalmology practices temporarily was a challenge. Now, practices are finding that reopening can be just as challenging and fraught with surprises (some unpleasant, a few positive).

Elizabeth Monroe, a partner and senior consultant at BSM Consulting Group in Phoenix, works with ophthalmic practices to help them through this process. (BSM Consulting offers a number of free resources for practices at their website: bsmconsulting.com/coronavirus-BSM-resources.) Here, she offers some observations and suggestions to help ease the return to a fully functioning operation.

"One of the things we've learned over the past couple of weeks is that reopening is affected by many factors," she says. "One factor is the size of the office. For example, in New York City, office space is at a premium. Physicians with very small offices can only have one or two patients in at a time and still maintain social distancing. They may not be able to see enough patients to allow them to pay their bills. Another factor is the age and overall health of the physicians. In some cases, the age and/or underlying health of the doctors puts them at greater risk of having extreme complications should they contract COVID-19, so they're just deciding to stay home for a while. Some are deciding to close their practices altogether and retire.

"In addition, some practices recently negotiated contracts with new young associates giving them a high salary and incentives based on production," she says. "Now, we're doing a lot of work helping practices revise employment agreements to a point at which it makes sense and is something the new provider can live with."

Ms. Monroe offers some key pearls for practices as they reopen:

• ***Make sure you have an in-house supply of PPE.*** "In fact, many of the states we're working in require a practice to have a multi-week supply of masks and protective gear in-house," says Ms. Monroe. "You can't be depending on some governmental agency to supply you with it."

• ***Do trial runs before patients come in.*** "Have your social distancing plan worked out in advance and try it to make sure it's workable before patients return," she advises.

• ***Review each patient's condition and decide what level of care is needed.*** "Identify what each patient needs," she says. "Then, create a matrix or scheduling tree using this information."

• ***Contact patients directly if you want them to come in.*** "Many patients will be afraid to come in," Ms. Monroe points out. "If you believe a patient really needs to come in, have the doctor call the patient directly, partly to go over the safety protocol, but also to share with the patient why an in-person visit is important. Practices relying on automated reminders during reopening are seeing a very high no-show rate."

• ***Don't expect all staff to jump at the chance to return.*** "Many staff members have multiple considerations when coming back," Ms. Monroe says. "They might be afraid, have child-care issues, or be in a higher risk category and concerned about contracting the virus. Staff members also seem more reluctant to come back if the office's working environment wasn't great before COVID. If a practice offers an employee the opportunity to return and the employee doesn't come back when recalled, document the reason the employee isn't able to return."

• ***Think carefully about who to call back first.*** "The number one thing you should do is look at your 'star performers,' including the people who are able to do multiple things in the office," says Ms. Monroe. "Those who have the most to offer should be asked back first.

"Ironically, working with a smaller, top-quality staff is helping some practices," she continues. "Some of them are saying, 'We're smaller but mightier.' It can be an eye-opening experience."

• ***Don't bring everybody back just because you can, even if you want to.*** "Many practices applied for and received the PPP loan and HHS stimulus money," says Ms. Monroe. "With those resources it's tempting to bring all staff members back in, but we suggest that practices analyze how many patients they can safely put through their office. Based on that volume, right-size your staff and cost structure. Don't recall staff without having work for them to do."

• ***Consider paying bonuses so staff won't earn less if they return.*** "The stimulus unemployment bonus has been a lifesaver for millions of individuals, but because it wasn't scaled up or down in response to each state's unemployment pay rate, it had the unintended side effect of making some people better paid if they're not working—for a little while, anyway," says Ms. Monroe. "We've been informed that you can use your PPP money for staff bonuses, so some practices have been offering bonuses to staff who are willing to come back. They make sure that staff who return are making at least the same money they'd make if they'd stayed home and collected unemployment."

• ***Put together a financial forecast for your practice.*** "This will give you a clearer picture of the variables you're dealing with and some idea of when you may be able to get back into the black," says Ms. Monroe. "This will help you understand what you need to do to sustain your practice in the meantime. If the variables change over time, you can tweak your forecast accordingly."

• ***Use telemedicine as much as possible.*** "This could be particularly helpful with patients fearful of coming in, and practices with limited space," she points out. "For example, one doctor might be able to work from home doing virtual consults and virtual exams. Some practices are creating hybrid exams in which the patient only comes to the office for diagnostics and testing. The doctor calls the patient later via video chat and provides the results of the testing and comes up with a treatment plan."

• ***Don't call it "telemedicine."*** "Many practices we're working with have indicated that patients don't respond well to the term 'telemedicine.' They often decline an offer to meet over video when that term is used," Ms. Monroe explains. "When it's presented as a chance to talk to the doctor or as a 'virtual examination,' patients seem more open to trying it."

• ***Script the telemedicine pitch for your staff.*** "The way this option is presented affects how many patients agree to see the doctor this way," says Ms. Monroe. "Also, patients need to know that there's a cost involved, just like a normal visit, but that you'll bill their insurance."

Ms. Monroe adds one last thing about video interaction with patients. "Physicians are telling us that even if they can't do all the diagnostic testing or a complete exam by video chat, their patients have been very grateful for being able to do this," she says. 'Their patients feel connected to them. They love that the doctor checks in with them. So it's definitely a plus for many patients."

Government Sues Regeneron

The U.S. Attorney's Office in Massachusetts recently announced that the government has filed a civil False Claims Act complaint against drug manufacturer Regeneron Pharmaceuticals.

The complaint alleges that "Regeneron paid tens of millions of dollars in kickbacks for its macular degeneration drug Eylea (aflibercept), using a foundation as a conduit to cover co-pays for Eylea."

For its part, in a statement Regeneron stated, "There is no merit to the civil complaint filed by the U.S. Attorney for the District of Massachusetts. It is unfortunate that a misguided lawsuit is attempting to assign wrongful intent to entirely legal conduct. Regeneron has fully cooperated with the government's investigation and will vigorously defend the company's case." REVIEW

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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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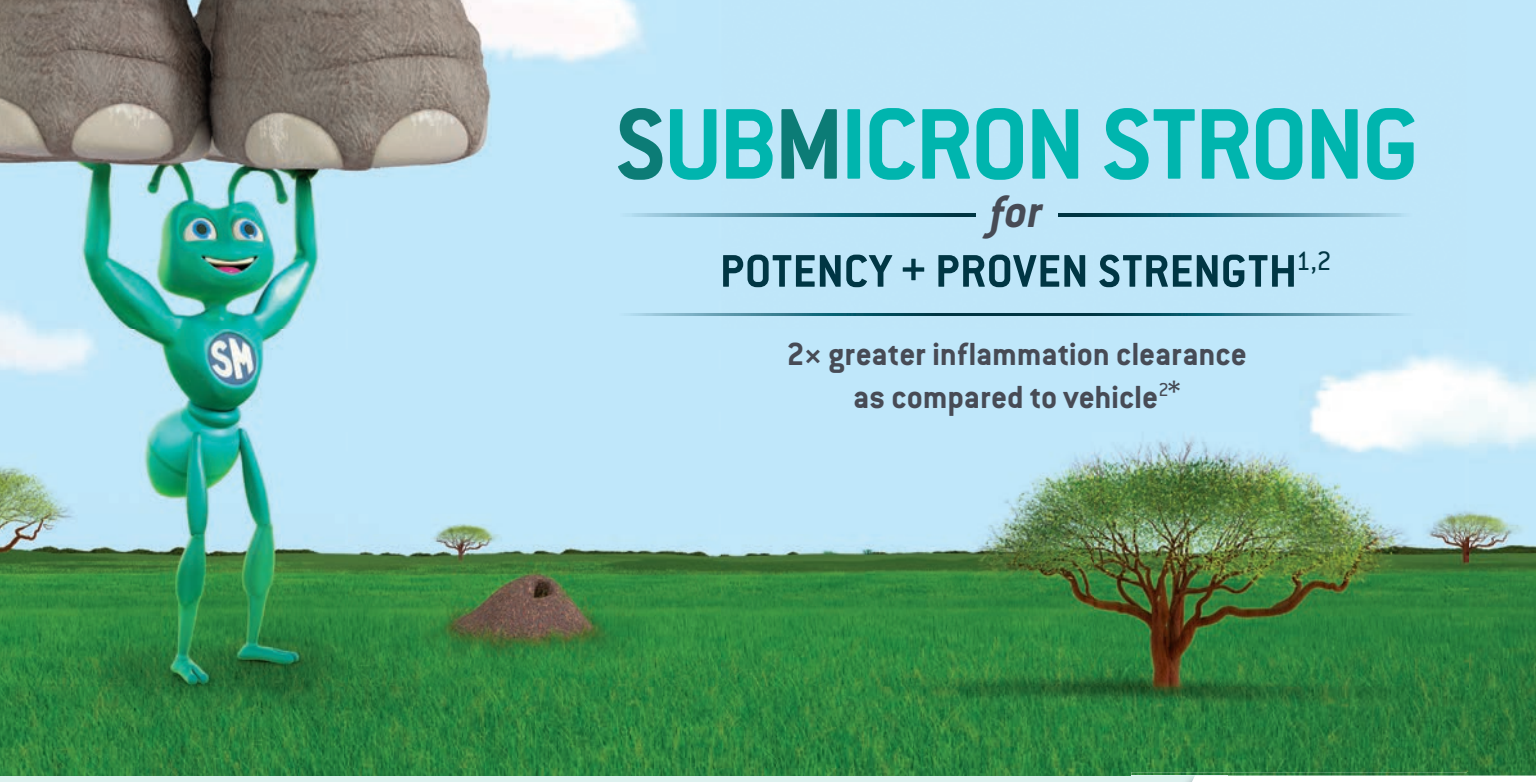

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†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

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

Indication

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

Important Safety Information

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

Important Safety Information (cont.)

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

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

Please see brief summary of Prescribing Information on adjacent page.

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

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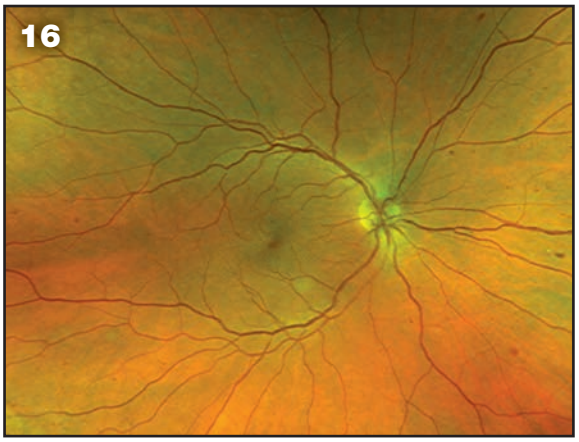

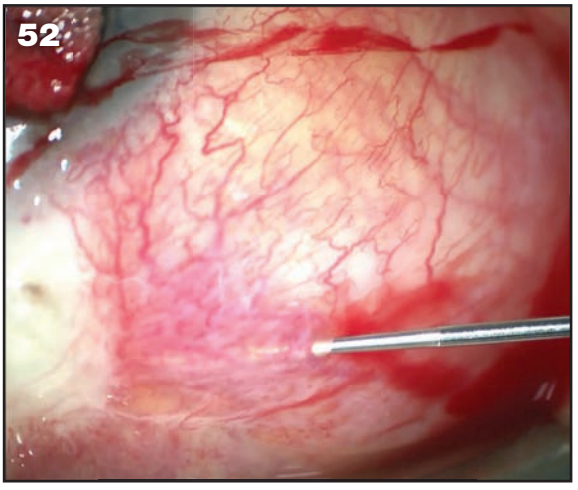


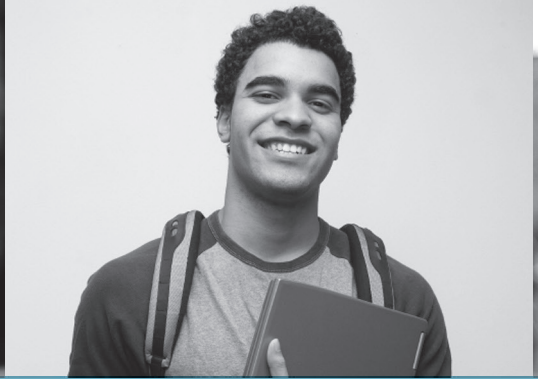


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Electronic Device Use in The Time of COVID-19

The use of devices among kids is increasing during the lockdown, but what are the long-term effects?

Krithika Venkatasubramanian and Aparna Ramasubramanian, MD, Phoenix

We know that the use of screens can have multiple undesirable effects on the eye. The pediatric eye is particularly susceptible to damage during the years of development and excessive screen time can result in both temporary and permanent afflictions. This is important to consider against the backdrop of the coronavirus pandemic, during which screen time has significantly increased. Here, we'll discuss common pediatric afflictions such as asthenopia, myopia and eye muscle problems, as well as recommendations from the American Academy of Pediatrics that can help your patients' parents regulate their children's screen time.

The Scope of the Issue

In the era of computers and smart phones, it is hard to imagine a task that hasn't been made easier by some sort of technology. Electronic gadgets and screens are being used more often, and children are exposed to devices at younger and younger ages. Our use of devices such as televisions, computers, laptops, e-readers and cell phones has increased exponentially over the past few decades. Reports have suggested that, in 2013, before age 8, 72 percent of children used digital tools compared to 38 percent in 2011. In children under 2, this percentage is even more striking, with electronic use increasing from 10 percent in 2011 to 38 percent in 2013.[1] In a recent survey of people ages 16 to 19, the average screen time was between five and seven hours a day.[2] In another study, children ages 3 to 11 played with an interactive screen for more than 30 minutes a day, and about half of that time was spent alone.[3]

Undeniably, the use of screens in our daily lives has multiple advantages. Electronic gadgets are portable, easy-to-use and can provide extensive amounts of information at the tap of a finger. However, despite these devices' usefulness, the extent to which the average child uses screens has raised red flags in terms of the effect it might have on his or her eyes. Amid the current pandemic, most schools in the United States have been forced to close, and the resulting use of alternative methods of teaching has forced the screen time of kids to increase drastically. Children are having to complete a school curriculum entirely on a screen. In addition, social distancing has decreased recreational activities, resulting in even more screen time. In light of these changes, it's important to take into account the effect these screens have on children's eyes and regulate the use of screens in order to prevent permanent damage.

Asthenopia

Asthenopia is a very common effect of excessive screen use, and is prevalent among both children and adults. It's commonly called "eyestrain," or "computer vision syndrome."

In a study involving 576 school-age children between 11 and 17 years old, 18 percent experienced eyestrain at the end of the day after working on digital devices.[4] Asthenopia is caused by a multitude of factors, including an imbalance of the extraocular muscles, accommodative insufficiency, uncorrected refractive error and improper lighting.[5] Reading distance also contributes significantly to the development of asthenopia. The ideal distance for reading and writing is considered to be between 30 and 40 cm; for a

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CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

References: 1. Sawhney AS, Jarrett P, Bassett M, Blizzard C, inventors; Incept, LLC, assignee. Drug delivery through hydrogel plugs. US patent 8,409,606 B2. April 2, 2013.
2. DEXTENZA [package insert). Bedford. MA: Ocular Therapeutlx, Inc: 2019.

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computer screen it should be 50 to 70 cm.[6] The reading distance for a smartphone is 20 to 30 cm—significantly closer than reading or computer distance—which causes a majority of patients to develop asthenopic symptoms after only an hour of use.[7]

In a study performed in China that involved 4,786 students, the prevalence of asthenopia was 53.3 percent and was positively correlated with the level of digital reliance and time spent on handheld devices at bedtime. Prevalence of asthenopia was negatively correlated with aerobic exercise duration.[8] The study suggested the following measures to prevent asthenopia: limiting the amount of time spent using digital devices in bed (less than 30 minutes); adopting a posture of lying on one's back while using digital devices in bed; and engaging in aerobic exercise for more than an hour per day.[8] Although asthenopia is a temporary condition, and often subsides after spending time away from the screen, the frequency at which a child uses the screen can affect the severity and rate of asthenopia. If persistent, symptoms of asthenopia can have deleterious effects on academic performance.

Myopia

The rapid rise in children's consumption of electronic media has occurred alongside another frightening trend: increases in childhood myopia.

The number of children with myopia in the United States has doubled in the past 50 years. Moreover, up to 90 percent of teens and young adults in Asia are myopic. The pathogenesis of myopia is multifactorial and includes genetic and environmental factors. One common hypothesis among scientists is that the light rays emitted by screens hasten eye growth, causing the eyes to become longer and more myopic earlier in life. Investigators collected data from 26,433 preschoolers as part of the Longhua Child Cohort Study performed in the Longhua District of Shenzhen, China, and found that screen exposure in early life might be associated with the onset of preschool myopia, with the strongest association being in the first year of life.[9] It's been clearly documented in randomized trials that spending time outdoors minimizes myopia progression.[10]

For children, however, the increasing time on the screen decreases the time available for outdoor activities. In the Netherlands, a study was undertaken to evaluate the effect of digital devices on myopia progression. This study evaluated 5,074 children born between 2002 and 2006 and measured the axial length and refractive error at ages 6 and 9. Questionnaires about electronic use were collected at ages 3, 6 and 9 years. This study found that "near work"—defined as a combination of computer use, reading time and reading distance—increased the odds for the

development of myopia at age 9. Outdoor exposure decreased these odds.[11] All of this collective data suggests that larger amounts of screen time during childhood may lead to myopia.

Strabismus

Eye alignment and the maintenance of stereoacuity is carefully maintained, in part, by the extraocular muscles. Some studies suggest a relationship between esotropia and excessive electronic use. Researchers reviewed the electronic records of 12 patients with acute acquired comitant esotropia and recorded the duration of smartphone use. Reduction in esodeviation was noted in all patients who refrained from smartphone use. Surgical correction was required in three patients for residual deviation after refraining from smartphone use.[12] This study raised a strong suspicion that excessive screen time can lead to strabismus and a subsequent loss of stereoacuity. Future studies are needed to better correlate the effects of device use on extraocular muscle function.

Blue-light Effects

Most electronics use backlighting for display screens, which gives off shorter wavelength, ultraviolet blue light rays. Though blue light rays directly from the sun can damage the retina, the blue light from screens is comparatively weaker. Though it can't directly damage the retina, this blue light can disrupt children's circadian rhythms and lead to sleep-cycle deregulation. When children watch screens right before bed, the blue light rays can throw off their circadian rhythm, making them feel more awake. This can lead to insomnia and interference with sleep schedules. Therefore, it's recommended that all device use be discontinued at least one to two hours before bedtime in order to reduce the detrimental effects of blue light on circadian rhythm.

Guidelines for Electronic Use

Despite the potential adverse effects of screen time on a child's eyes, it's not practical to cut off screen time for children altogether. Rather, a balance must be achieved in which the child is still able to access screens without it posing a harm to her health.

To this end, the American Academy of Pediatrics has proposed a set of guidelines for managing a child's screen time.[13] The AAP advises that children under 18 months shouldn't be exposed to screens (other than for video calls). They suggest that children between 18 months and 5 years watch no more than one hour per day of digital content. Programming should be educational, prosocial and include parental interaction for children to reap the most benefit during this time of critical brain development. Children ages 6 and above may have more liberal screen time use, but within reason. The AAP also recommends that families should try to implement "positive" screen time, which involves the family watching together so that the time is more interactive. In addition, for older children, it's recommended that screens be located centrally in the house so that content can be monitored. Finally, the AAP recommends that parents should impose specific times at which their children unplug and engage in non-screen activities.

In conclusion, excessive use of screens in childhood can have many negative effects. Unregulated amounts of screen time may lead to ailments like asthenopia, myopia and disrupted oculomotor function. Greater information regarding the effects of screen time on eye and vision development will be immensely valuable, given the increasing presence of electronics in our daily lives. This is especially important during the coronavirus pandemic when screen time for children has escalated dramatically. (Data from Axios suggests that tablet use has tripled and cell phone usage has doubled during the pandemic.[14]) By following the guidelines from the AAP and regulating screen time for children, parents can ensure safe and reasonable screen usage for their children. REVIEW

Dr. Ramasubramanian is a pediatric ophthalmologist, and is medical director of the Phoenix Children's retinoblastoma program. Ms. Venkatasubramanian is Dr. Ramasubramanian's research assistant.

Neither author has a financial interest associated with the article.

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10 Practical Problems During the Pandemic

Doctors share their solutions for 10 pandemic-related practical problems you'll likely encounter.

Christine Leonard, Associate Editor

While the global pandemic has brought about certain overarching changes to daily life such as hypervigilance, quarantine, social distancing and the resulting decline in patient volume and elective surgeries, it's also caused several more mundane, but no less important, problems that you might not have been expecting: Have your oculars been getting foggy with all the mask-wearing, for instance? In this article, we've rounded up some creative solutions for 10 common problems you may run into in the clinic and the OR as a result of the pandemic.

1 Maintaining social distancing in the clinic. Standing six feet away from everyone else doesn't come naturally for most people and is easy to forget in the absence of reminders to maintain physical distance. In order to comply with social distancing and reduce the chance of viral transmission, practices have had to reduce patient volume and find new ways to keep those who do visit the office safe and separated from others. Here are some ways doctors are helping their patients maintain social distance.

—Pre-filling forms. "We've started having people fill out their history and medications over the phone beforehand," says Joshua Frenkel, MD, MPH, of the Wang Vision Institute in Nashville. "We have staff calling our patients to fill out as much information before they arrive as possible," he says. "It cuts down on wait times and improves the efficiency of our clinic."

—Musical chairs. Sometimes all it takes is a simple solution. "For social distancing, we've moved our waiting room chairs six feet apart," says John Jarstad, MD, FAAO, a professor of clinical ophthalmology and director of cataract and refractive surgery at the University of Missouri Mason Eye Institute. Some practices have also put upholstered furniture into storage and are using plastic chairs instead, which can more easily be sanitized after patients use them.

Michele C. Lim, MD

Michele C. Lim, MD, uses a Tonopen with a sterile cover to check a patient's pressure at her drive-up eye exam clinics.

—Restaurant buzzers. Michele C. Lim, MD, professor, vice chair and medical director of ophthalmology

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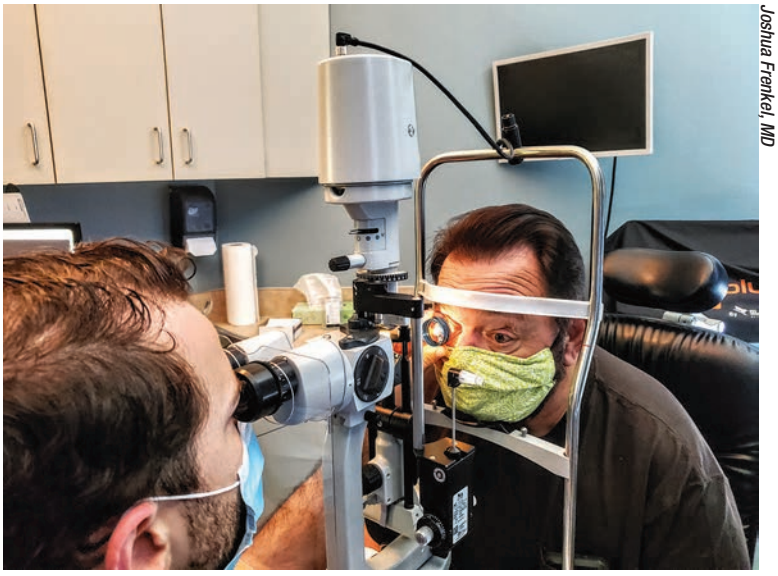
at the University of California Davis in Sacramento, uses restaurant reservation buzzers to help limit the number of people crowding the waiting room. "If the waiting room looks busy, patients will be given buzzers so they can roam around our outpatient building or go back to the parking lot [while they wait]," she says. She points out that this method works well for the elderly, who may not be able to use or receive text message alerts. Additionally, the restaurant buzzers operate on a radio frequency, which works in a parking garage, unlike Wi-Fi.



Joshua Frenkel, MD

Joshua Frenkel, MD, MPH, examines a patient with a 90-D lens. He says that gently pressing down on your patient's mask can help to prevent the lens from fogging.

—Drive-thru exams with video follow up. Dr. Lim has begun offering drive-up visits to decrease the number of people in the office. "Video visits on a phone camera don't allow us to see the detailed structures of the eye, but with a drive-up exam, we can obtain some objective data," she says. Patients drive into the parking lot and sit in their cars while Dr. Lim checks vision and pressure. Then patients return home and a doctor follows up with a video visit to go over their care.

2 ***No-visitor policies aren't always ideal***. Many hospitals and offices have instituted no-visitor policies to help cut down on the number of people in a health-care setting, but this often means that patients are left without the assistance they need for emotional support, translating or remembering important information. Amir H. Marvasti, MD, of Coastal Vision Medical in Orange County, California, says this is especially true for the elderly. "We almost never allow another person to come in with the patient," he says, "but if I feel like they'll forget the information, or if the patient needs help with translating or decision-making, we have a phone call with their trusted support person."

Dr. Jarstad adds that "no HIPAA laws are violated in this instance if the support person is a family member and you obtain permission. We have family members wait in the car, but they can also talk to us on the phone or come in if the patient insists on it. But they must wear a mask and are screened at the door before they come in."

3 ***Telehealth technology challenges with some patients.*** A large percentage of ophthalmic patients are elderly and may have trouble with the technology required for their virtual exam. Here are a couple of ways you can help ensure the virtual visit runs smoothly, tech-wise.

—A simple checklist. Sending patients a simple tech checklist along with the usual instructions for accessing the telemedicine virtual video visit can help your patients be more prepared for their exams and can save you valuable time. Some checklist items might include testing the video camera and microphone settings with a website program, guidelines on how to position or hold the camera, and ensuring good lighting.[1]

—A run-through with a staff member. Nikola Ragusa, MD, FACS, of the Bronx Eye Center in New York, says, "Since this is still a relatively new way for doctors to see patients, it's good to have a staff member call prior to the video visit to go over the nuances of the telemedicine service that's being used. Some are more intuitive than others, and for some patients nothing is intuitive enough. Camera and microphone access is critical for these encounters. Knowing how to log onto a call and ensuring that lighting, as well as video and audio quality, are adequate are key to a successful and frustration-free video visit. Most of these elements can be handled by a staff/technician prior to the call. Having said that, a good script is important for the staff member along with a checklist for the patient."

He adds that having a back-up plan, such as FaceTime or Google Duo, is important in case your telemedicine service doesn't function. "It's better to overprepare and let the patient know ahead of time that a backup service may be used for the encounter," he says.

4 ***Lens fogging***. With mandatory masking in place, lens fogging has become a major problem for ophthalmologists during the pandemic. Not only do eye glasses fog up with most masks, but oculars and diagnos-

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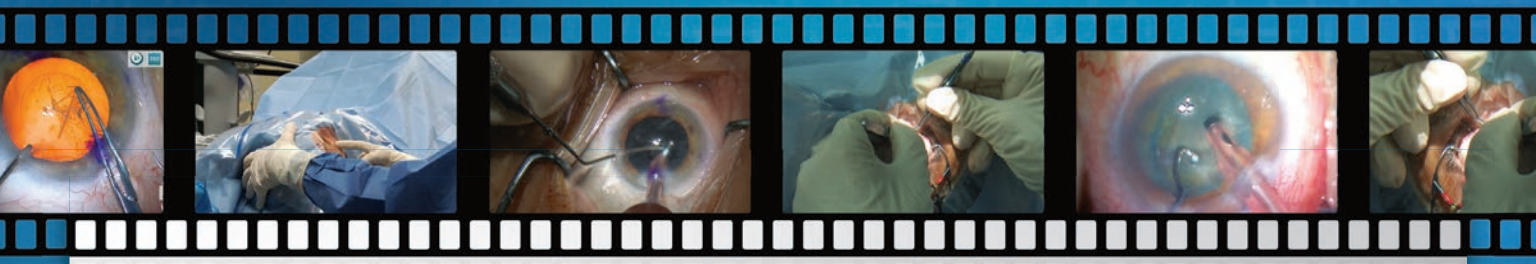

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John Jarstad, MD

A complimentary slit lamp shield from Carl Zeiss Meditec AG. Zeiss offered two free slit lamp shields per practice through May 2020. (The company notes that these breath shields aren't approved medical devices.)

tic imaging tools also fall victim to lens fogging.

"Doing a good dilated fundus exam has been tricky," says Dr. Marvasti. "My oculars get foggy with my mask, and then as I'm holding the lens close to the eye of the patient who's also wearing a mask, the lens fogs up. Unless there's a tight seal on the mask, there will be fogging. For routine visits, this isn't a major problem, but if I'm trying to find a small tear or if I really need the best visualization and need to take my time, the lens fogging can be frustrating." Here are three ways you can cut through the fog.

—Paper tape or gentle finger pressure. If you don't have the type of mask that can make a tight seal, such as an N-95 mask with a metal piece that molds to the shape of the nose, Dr. Marvasti recommends putting surgical tape over the top of the mask to prevent fogging of the lens. This approach can be time-consuming, he admits. "If you have 20 patients, doing this for every one of them might take too long," he says. He says that for larger patient volumes, "I press my ring finger gently on the mask to push it against their skin, which mechanically creates a tight seal so their breath doesn't come up toward the lens. I've had some success with that."

—Dishwashing liquid. "I just ran into a brick wall when I was trying to do delicate YAG lasers on posterior capsules," says R. Bruce Wallace III, MD, FACS, founder and medical director of the Wallace Laser and Surgery Center in Alexandria, Louisiana, and a clinical professor at Louisiana State University and Tulane University School of Medicine. "I couldn't see anything because the lenses for the slit lamp, the laser and the lens on the patient's eye had all fogged up," he says. Dr. Wallace went online and discovered that dishwashing liquid might hold the answer. "You spread the soap on the surface of the oculars and then wipe or buff it off," he explains. "Suddenly, it's clear. No more fogging. It makes a huge difference."

Soap can prevent fogging because the surfactants reduce water's surface tension. Otherwise, water molecules clump together in tiny droplets on the lens surface, creating lens fog. Leaving behind a thin surfactant film on your lenses will reduce any water surface tension and allow the water molecules to disperse evenly across the lens surface in a transparent layer.[2]

—Anti-fog sprays. Dr. Jarstad, a former competitive downhill skier, says that anti-fog sprays are widely available at ski shops, sporting goods stores and online to prevent lens fogging. Small, portable bottles of anti-fog spray run in the $8- to $15-dollar range online.

5 ***Many slit lamp shields aren't large enough.*** "We have clear plastic Zeiss shields that measure 10 by 12 inches on our slit lamps now, but simulation studies have suggested that if a patient were to sneeze or cough with this size shield, about 50 percent of the aerosol would pass around the shield,"[3] says Michael Colvard, MD, of the Colvard-Kandaval Eye Center in Encino, California. "That's a bit of a concern, but the problem is that slit lamp shields that are much larger begin to interfere with the clinical exam, especially indirect ophthalmoscopy with hand-held 78- or 90-diopter lenses, or gonioscopy."

Larger slit lamp shields are available for purchase, but if you prefer the DIY route, Dr. Jarstard says you can buy quarter-inch thick, clear plexiglass sheets from your local hardware store to make your own. "Slit lamp shields can be made at home by anyone with a bandsaw or jigsaw and a power drill with a two-inch bit," he says. "The Zeiss-donated shields have two-inch holes, placed 0.75 inches apart for the oculars. The shields fit easily over the oculars with enough room to adjust the oculars for proper individual interpupillary distance."

6 ***Obtaining IOP.*** Concerned with contamination, many practices have stopped using Goldmann applanation to monitor patients' pressures. "We use the Tonopen with a sterile cover for each patient," Dr. Jarstard says.

"We're leaning on the Tonopen for most routine visits," adds Dr. Marvasti. "If I'm trying to get accurate measurements for a glaucoma patient or assessing whether MIGS or drops

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will be sufficient, I'll make an exception and check the Goldmann applanator. If I need to use the Goldmann, I try to use it on only one patient per day and clean it very well afterward."

7 ***Potential diagnostic artifacts***. This is another problem resulting from mask-wearing. The ASCRS Glaucoma Clinical Committee made a cautionary statement to its members on May 29 about this new potential concern. David Palmer, MD, of Northwestern University, found that condensate on perimeter lenses could create visual field changes that could be interpreted as a sign of progression. ASCRS suggested applying hypoallergenic tape to seal the top of the mask during perimetry to prevent condensate, repeating visual fields if disease progression is suspected and to be aware of possible errors due to fogging during other ocular diagnostic tests such as OCT and autorefraction.

8 ***Risk of viral transmission in the clinic.*** Good sanitization and cleaning procedures have always been important for practices, but these concerns are front-and-center during the pandemic. Here are some reminders for playing it safe.

—Sanitize everything. Steve Charles, MD, of the Charles Retina Institute in Germantown, Tennessee, says that disinfecting equipment, using face shields and slit lamp shields, washing 90-D lenses and indirect lenses with soap and water can all help reduce transmission.

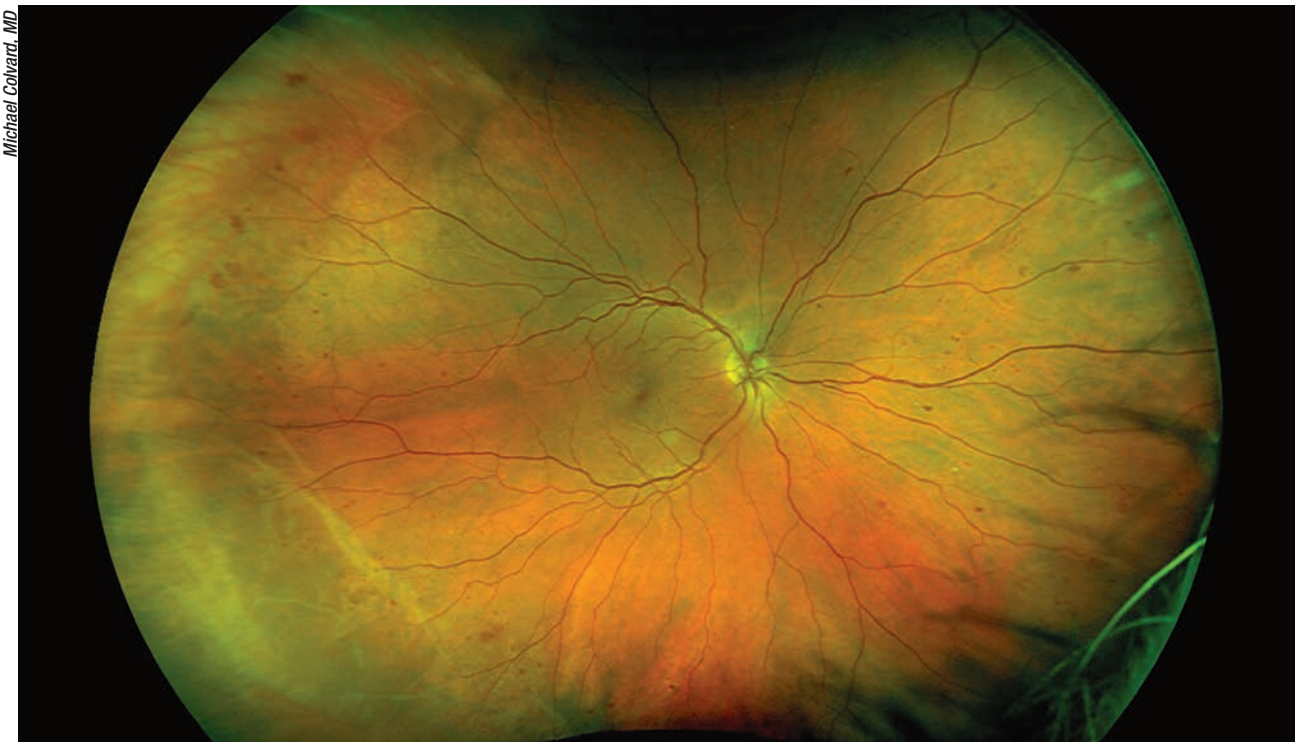
"For some in-office procedures like YAG and SLTs, there's a lens that comes in contact with patients' eyes," Dr. Marvasti says. "I'm trying to limit those procedures to one a day, and I use a particular lens on a particular patient. Even if I clean it properly, I'm worried that I may still cause transmission of a virus." Leaving the lenses overnight to allow any residual virus to die off takes extra time, but Dr. Marvasti says he prefers to play it safe.

Dr. Jarstard says he washes his YAG and SLT lenses with soap and water and then wipes them down with peroxide or alcohol wipes and leaves them to dry.

—Check manufacturer guidelines. Not all instruments and devices can be disinfected the same way. Checking with instrument manufacturers on the best ways to clean and disinfect is advised. For example, Zeiss has published specific guidelines on its website for disinfecting instruments like Humphrey perimeters. The company recommends cleaning this device with a fine mist of 70% isopropyl alcohol, without rubbing and without any use of UV-C light.

—Rely on other imaging. "I don't think any of us would be keen to do direct ophthalmoscopy now, which involves being virtually face to face with the patient," says Dr. Colvard. "I don't imagine that the patients would be very happy with this kind of exam either. But even with

Michael Colvard, MD



A fundus photo of a patient with nonproliferative diabetic retinopathy taken with an Optos fundus camera. Relying more on imaging devices allows doctors to look at the retina without being face-to-face with the patient.

indirect ophthalmoscopy the physician is no more than a foot and a half away from the patient, and a thorough exam means prolonged exposure. For this reason, we're finding ourselves doing more posterior photographic imaging and OCTs than we were doing before the pandemic."

Risk of viral transmission in the OR. Many states require COVID-19 testing prior to surgery, but Dr. Frenkel says that at this point, it isn't terribly useful. "I think it's a great idea in theory," he says. "But we're having trouble testing right now, nationally, and there are many logistical hurdles. It would be more useful if we could get same-day results. A test will only tell you whether or not your patient was negative or positive at the time of the test. If your patient tested negative, by the time they come in for surgery, they could have become infected."

Dr. Charles shares some of his basic COVID safety requirements for surgery. "These are necessary to reduce risk to staff, but they're not sufficient to eliminate the risk," he cautions:

—Airway management. SARS-CoV-2 poses a risk to staff through aerosolization. Dr. Charles says that "endotracheal intubation is safer for anesthesia staff than laryngeal mask airways. Additionally, oxygen masks and nasal cannula tubes must be handled with gloves after use, as they pose a high risk to staff. We've always used oxygen masks on all monitored anesthesia care cases and vacuum lines under drapes to prevent CO_2 retention under the drape and to reduce aerosol spreading of viral particles."

—Nasopharyngeal swab. It's important to determine whether or not your patient has active infection. However, as Dr. Frenkel notes above, the timing of the test before surgery and the time it takes to get results can present problems. Additionally, Dr. Charles says, "There are many non-validated tests on the market."

Dr. Colvard adds that testing requirements vary by state and can change from week to week. "When we began to do elective cataract surgery again, the general standard of the community was to require all elective surgery patients to undergo COVID testing three days before the procedure," he says. "More recently in Los Angeles, most eye surgery centers have changed the requirements so that cataract surgery patients don't need testing unless they're likely to require airway support. So cataract patients in our community who are afebrile, asymptomatic and have no history of COVID exposure aren't required to undergo preoperative COVID testing. Patients who are undergoing some oculoplastics procedures who are likely to need airway support, however, are required to undergo preop testing."

—Serology for previous infection. This presents similar problems to nasopharyngeal swab testing, says Dr. Charles. "There's a delay between infection and positive serology, and it takes a while to get results," he says.

—Drape the microscope. Asymptomatic infected staff are at the highest risk of transmitting COVID-19 to the patient. Dr. Charles always drapes the microscope on every case. He adds that it's important to "disinfect the bottom of the microscope optical head after each case and clean the objective without damaging the AR coating."

10 ***Plume from phacoemulsification.*** "The ultrasonic vibration of the phaco tip causes cavitation and bubbles in the anterior chamber," explains Dr. Colvard. "The recent concern has been that this cavitation might create a spritz of viral organisms that might leave the eye around the phaco tip and enter the OR environment."

A group at the Bristol Eye Hospital used special photography techniques to better visualize aerosolized particles in their investigations on a plume during phaco. You can view video at youtu.be/8LGwI9LIYmU. Here are some of the group's findings and recommendations:

—Povidone-iodine. Povidone-iodine reduces any theoretical viral load on conjunctiva, says the Bristol group.

—A smaller incision size. In the study, a 2.2-mm wound reduced visible aerosol, whereas a 2.75-mm wound allowed aerosols to escape. Ike Ahmed, MD, of the University of Toronto and the Prism Eye Institute in Ontario, also demonstrated that there was no evidence of visible aerosolization with a 2.2-mm incision. (You can view his video at youtu.be/GHH_rvyarCI). Commenting on Dr. Ahmed's video, Douglas Wisner, MD, of Wills Eye Hospital in Philadelphia, says he "recorded a case under high magnification with a 2.4-mm incision to look at the same thing . . . No aerosolization was noted."

—Hydroxypropyl methylcellulose. The Bristol group found that applying HPMC every minute during active phaco prevented aerosolized particles from escaping a 2.75-mm wound. "Does this impair visualization?" asks Dr. Colvard. "In surgery the other day, I put methylcellulose on the cornea just to test it," he says. "You need to smooth it out a little bit, but it doesn't impair visualization. You can see quite well through it. So if one uses a 2.75-mm incision and has concerns based on the 2.75-mm incision demonstration by the Bristol group, then the use of topical methylcellulose seems reasonable. The only caveat is that one needs to wash all the methylcellulose off the cornea before taking ORA measurements."

—Irrigation and aspiration for at least six seconds. The group found that performing I/A for at least six seconds before starting active phaco helped to reduce aerosols.

Dr. Frenkel notes that many of the Bristol group's recommendations, such as using small incision sizes and doing I/A prior to the procedure, are already routinely done by eye surgeons. "More studies are needed before everyone undergoes a massive change in practice and starts applying HPMC to the wound every minute," he says. "I also think it's important to have more studies done in human eyes." The Bristol group performed their investigations using a human corneoscleral rim mounted on an artificial chamber. The phaco device was kept in a fixed, static configuration to reduce variables.

Uday Devgan, MD, of Devgan Eye Surgery in Los Angeles, says some of his colleagues from the University of Toronto also did experiments to determine whether cataract surgery posed a risk of viral exposure. The Toronto group used trypan blue to simulate viral aqueous in a human cadaveric eye. You can view the video at youtu.be/epcDtNN-PkI.

In the first technique, I/A was done to replace the AC volume, prior to filling the AC with dispersive OVD. No aerosolized trypan blue dye was observed during torsional, torsional-longitudinal or longitudinal phaco. In the second technique, the 'viral' trypan blue aqueous was replaced with OVD prior to phaco. Dr. Devgan says that replacing the AC contents with OVD effectively evacuates the virus. No aerosolized trypan blue was observed during phaco. In the third technique, an open-sky model, performing phaco in BSS confirmed an aerosol plume. Dr. Devgan suggests removing the aqueous with I/A or evacuating the AC with viscoelastic at the beginning of the procedure. Neither longitudinal nor torsional phaco generates significant aerosols in a closed procedure, he says.

Dr. Colvard wonders about the clinical impact of such findings. "The overarching question is what significance do these experiments have?" he says. "Most surgeons use 5% Betadine to sterilize the surface of the eye prior to cataract surgery. This concentration of Betadine kills 99 percent of organisms, including, as I understand, the COVID virus. Then most of us empty the anterior chamber volume completely and fill the anterior chamber with OVD. So it's hard to imagine that a lot of organisms, even if a patient were infected, would end up entering the OR from this source. If one has the bad luck of operating on a patient with an active COVID infection, it seems logical to assume that the risks of aerosolization from the patient's own respiratory system would constitute a far greater risk." REVIEW

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

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

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

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

Delayed Healing

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

Exacerbation of Infection

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

Cataract Progression

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

ADVERSE REACTIONS

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

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

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

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DEXYCU (dexamethasone intraocular suspension) 9%,
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

Removing Hard Cataracts Safely

A group of surgeons in India uses a novel technique to reduce endothelial cell damage and postop corneal edema.

Sean McKinney, Senior Editor

As you know, the challenges are many when you're confronted by a hard, intractable and leathery cataract that's difficult to disassemble. High on the list of difficulties, of course, are the potentially perilous use of phacoemulsification, predisposition of the posterior capsule to rupture and the possibility of a traumatized corneal endothelium.

Surgeons at the Dr. Om Parkash Eye Institute in Amritsar, Punjab, India, routinely take on these cases by employing what they describe as a chopper scaffold technique, effectively removing the cataract while sparing the eye unnecessary damage. By reading this review of their approach, you can decide if you want to include it in your surgical arsenal and, if so, how you can implement it.

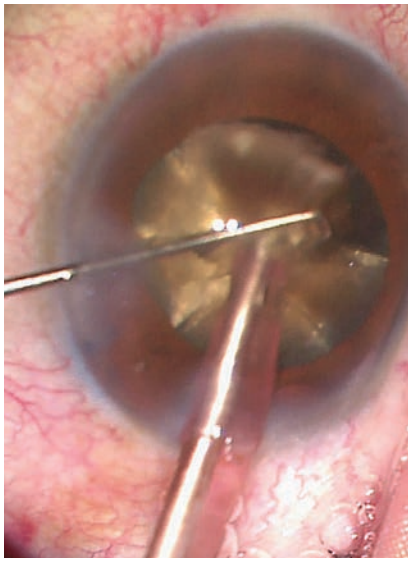
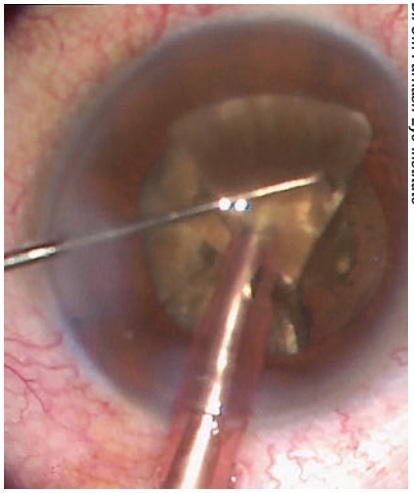


Figure 1. The sideport incision is made 60 to 80 degrees from the main port. This will optimize positioning of the chopper.



Dr. Om Parkash Eye Institute

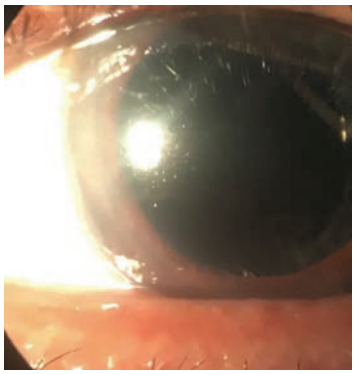
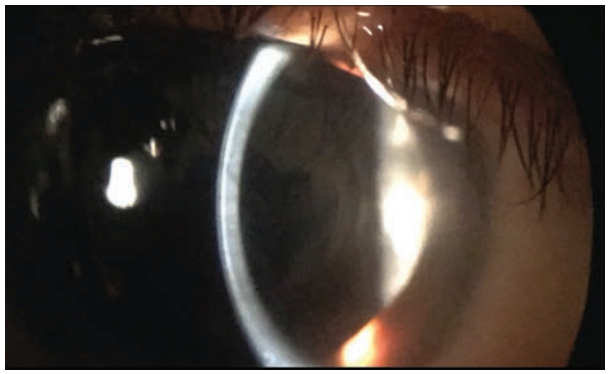
Figure 2. The junction of the shaft and the tip and adjacent parts form a shield that's horizontal and anterior to the nuclear fragments. The surgeon emulsifies spilling nuclear fragments and uses the phaco foot switch in a controlled manner, shielding nuclear fragments. The chopper shaft, shaft-tip junction and rest of the tip combine to prevent nuclear fragments from bouncing toward the corneal endothelium.

Familiar Consequences

Like you, Rohit Om Parkash, MS, head of the department of cataract services and chairman of the Institute, is all too familiar with the potential unwanted consequences of not breaking up a hard cataract effectively and struggling through even a good procedure to ensure a trouble-free extraction with as little disruption as possible. That's why his team has developed a technique that responds to the specific challenges of difficult phacoemulsification and potential corneal endothelium trauma.

"We know that increased ultrasound usage causes endothelial cell loss because of mechanical and thermal injury from ultrasonic waves emanating from the ultrasonic tip," he notes. "In addition, we also see mechanical trauma caused by nuclear fragments

and instrumetation. In hard cataracts, we must also respond to an environment of high fluidics. The hard fragments of the cataract are irregularly-shaped and rigid. It's important to remember that these pieces don't mold suitably at the phaco tip. As a result, we see uncontrolled scatterings of fragments, causing damage to the corneal endothelium in these cases."

Figures 3 and 4. These two slides show a clear cornea, as seen on the first postop day.

In concert with these effects are related risk factors that predispose the patient with a hard cataract to posterior capsule rupture because of zonular weakness, he adds. "The zonular weakness makes the bag floppy," he points out. "The use of high fluidics, in turn, predisposes the eye to post-occlusion surge. At times, those sharp nuclear fragments can cause collateral damage to the posterior capsule."

In this environment, adds Tushya Om Parkash, MS, director of the cataract and refractive department at the Institute, instrumentation that you can normally use quite safely poses a risk

"The use of blunt instruments, unintended insertion of instruments between the corneal stroma, Descemet's membrane, improper incisions and tight main incisions can all cause damage in these cases," says Dr. Tushya Om Parkash. "Damage to Descemet's membrane during irrigation and aspiration and during insertion of an IOL or phaco probe can also occur. These problems, along with the potential inexperience of a surgeon, are but a few of the intraoperative risk factors."

Standard Remedies

Shruti Mahajan, MS, a member of the practice at the Institute, notes that applying current concepts in practice that minimize the risks of ultrasound usage in a hard cataract are important to keep in mind.

"These include direct phaco chop and the use of power modulations and torsional settings (in which the phaco tip oscillates in a rotational manner along its primary axis) that use a variable pulse and burst mode," says Dr. Mahajan. "Another big help when removing hard cataracts is the use of phaco tips with decreased amplitude near the incision."

Meanwhile, Dr. Rohit Om Parkash emphasizes the need to focus your efforts on minimizing mechanical endothelial trauma at all times. He recommends employing the following approaches:

- use of endocapsular or deeper-plane phacoemulsification of totally separated small nuclear fragments;
- hypothermic perfusion;
- fluidics to provide a stable anterior chamber;
- use of an anterior chamber maintainer;
- replenishment of the anterior chamber with a visco-dispersive device; and
- relying on a femtosecond laser or manual pre-chopping techniques.

To address predisposition to endothelial trauma, he remains ever mindful of the reckless nature of those nuclear fragments, which all too often defy attempts to use the phaco tip carefully.

"Despite the energy modulations you may use, it's important to be constantly vigilant, mindful that the rigid and irregular nuclear fragments won't mold well at the phaco tip," he repeats. "Normally, of course, the nuclear pieces, with the use of fluidics, mold well with the phaco tip and are aspirated. We become accustomed to this. But when the nuclear pieces don't get aspirated, they can quickly get pushed off of the phaco tip by the ultrasonic power of the phaco unit, creating chatter and poor followability. This activity results in sharp nuclear fragments bouncing off of the tip in an uncontrolled way and hitting the corneal endothelium, resulting in significant endothelial cell loss."

Dr. Rohit Om Parkash notes that in cases of an increased anteroposterior diameter of the nucleus and a shallow anterior chamber, the working space in the anterior chamber poses an additional challenge for the surgeon. "This can increase the risks of chatter-related endothelial injury," he says. "Sometimes a misdirected stream of fluid can also predispose Descemet's membrane to detachment. Yes, dispersive OVD helps in shielding endothelial cells. However, the shield is temporary and there can still be endothelial injury."

The Chopper Scaffold

When they developed the chopper scaffold technique, the senior Om Parkash says the goal of his team

members was to use a common chopper as an alternative to dispersive OVD. They rely on the chopper, not dispersive OVD, to shield the corneal endothelium. "The positioning of the chopper must be between the phaco tip and the corneal endothelium when you're using this technique," he explains. "The shaft of the chopper, along with the phaco tip, mechanically shield the corneal endothelium from the chattering of the hard and pointed nuclear fragments. Our simple technique is easy to adopt, and it results in pristine clear corneas on postop day one. It requires neither a longer surgical time, with different phaco parameters, nor unique surgical preparations."

Dr. Tushya Om Parkash describes the technique in more detail. "You begin by making a sideport incision 60 to 80 degrees away from the main port," he says. "This facilitates ideal positioning of the chopper. Part of the chopper forms a junction with the tip of the phacoemulsification probe. Parts of the chopper and the phaco tip are primarily used to form a shield by horizontally placing the parts in a position that's anterior to the nuclear fragments."

While applying the technique, he says you will need to demulsify the spilling nuclear fragments. The foot pedal needs to be used in a controlled way as you shadow (shield) the fragments with the chopper shaft, the shaft-tip junction and the rest of of the tip, preventing the fragments from bouncing toward the corneal endothelium."

He also recommends the use of a thin chopper, which won't obscure your view of the surgical field. Otherwise, he continues, "you don't need to select any specific type of chopper. The routine chopper that you use will suffice. You also don't have to be concerned about overcoming any learning curve when adopting this technique. You just need to be careful to shadow (shield) the nuclear fragments around the phaco tip by placing the chopper in a near horizontal plane. You should be able to easily incorporate this technique into your surgical routine without any fuss.

"Our initial experience has yielded very clear corneas in the immediate postop period and acceptable levels of endothelial cell loss," Dr. Tushya Om Parkash adds. "The results of a study we performed reveal a significant benefit for the surgeon and the patient compared to the results we might have seen if we hadn't used this technique in these hard cataract cases. The levels of endothelial cell loss when using our phaco-based chopper scaffold approach are comparable to the low levels seen in femtosecond-laser-assisted cataract surgery."

To view a video of the chopper scaffold technique that these doctors presented at the ASCRS Virtual Annual Meeting on May 16, you can click on the following link and search for "Chopper Scaffold Technique" in the CME section: ascrsvirtualmeeting.ascrs.org

(Make sure you have a username and badge number for the virtual meeting.)

Testing the Technique

To validate the success they achieved in a few patients when using the chopper scaffold technique, the surgeons at Dr. Om Parkash's

(Continued on page 38)

Four Other Approaches to Hard Cataracts

Below is a summary of four alternative strategies to consider.

1. ***Individualize surgery.*** Specific surgical steps that have been individualized to the characteristics of a dense, hard cataract have been proposed as a way to enable you to achieve a more successful removal of the cataract and potential restoration of vision, surgeons say. Measures include preoperative history, physical exam and diagnostics that allow selection of the best incision, anesthesia and surgical technique for each dense nuclear challenge.[1]
2. ***Use a femtosecond laser.*** Compared to conventional phacoemulsification, the use of femtosecond laser-assisted cataract surgery for hard nuclear cataracts was found in one study of 95 eyes to conserve phacoemulsification power, providing a significant reduction in corneal endothelial damage and leading to faster visual rehabilitation.[2] Compared to conventional phacoemulsification cataract surgery, femtosecond laser-assisted cataract surgery has been shown to decrease the risk of anterior capsule tears in white cataracts, especially in type I cases, in a study of 132 eyes of 132 patients. The laser enabled more precise capsulotomies and better-centered IOLs. However, the laser didn't reduce the incidence of posterior capsule rupture.[3]
3. ***Try the "retrochop" technique.*** Performed under topical or local anesthesia, retrochop presents a way to divide a rock-hard nucleus by approaching its posterior and impaling it toward the phaco tip, allowing complete and efficient fracture of the lens. The technique relies on the use of a new chopper design and offers a short learning curve.[4]
4. ***Use hypothermic perfusion.*** In a study that involved 40 rabbits and 80 patients, hypothermic perfusion in phacoemulsification of hard nuclear cataract was found to be safe, effectively protecting corneal endothelium, decreasing corneal edema and reducing anterior chamber inflammation in the early postop stage.[5]

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Make the Most Of Your SMILE

Majid Moshirfar, MD, Salt Lake City

An expert SMILE surgeon shares his experience now that the procedure has been available for a while.

Though small-incision lenticule extraction has been available for several years now, it's still finding its niche in refractive surgery practices. Due to the way it reshapes the cornea without the use of a large diameter flap, SMILE may be a good choice for very active patients who might be at risk for a flap dislocation, as well as for patients who are at risk for severe dry-eye issues resulting from LASIK's larger-scale severing of corneal nerves.

Here, I'll describe the patients with whom I've had the most success with SMILE, and the techniques I use to ensure the best outcomes.

Patient Selection

Many of the qualifying factors I use for SMILE come from the LASIK patient-selection process.

As a quick review, SMILE is approved for between -1 and -8 D of myopia, with myopic astigmatism up to 3 D. The procedure can only be done with the Zeiss Visumax femtosecond laser. After docking the laser on the patient's eye, the surgeon uses it to create an intrastromal lenticule by making a posterior and anterior cut. The laser is then used to create a small side cut in the cornea. Using manual instruments, the surgeon dissects the lenticule from the surrounding tissue, then removes it. This removal of the lenticule induces the refractive change.

With the mechanism of the procedure now described, here are the main factors that influence my decision to perform SMILE:

- ***Ectasia risks.*** Among the prospective patients who fall into this refractive range, I also consider the corneal thickness. In the United States, we can't make the overlying SMILE cap thinner than 120 µm—since it's 120 µm thick—so as long as the residual stromal bed is thicker than 250 µm, the FDA allows SMILE to be done on that patient. I try not to go below 275 µm of residual stromal bed.

However, I also like to determine the "percent tissue altered," a LASIK safety metric first introduced by Marcony Santhiago, MD, of Sao Paulo, Brazil, several years ago. PTA is basically the sum of the flap thickness plus ablation depth, divided by the central corneal thickness. Dr. Santhiago has argued that a PTA of 40 percent or greater is a risk factor for the development of ectasia postop. I'm more conservative in my practice, so if a patient has normal topography and tomography, and has less than 38 percent of the tissue altered, I'll feel comfortable performing SMILE.

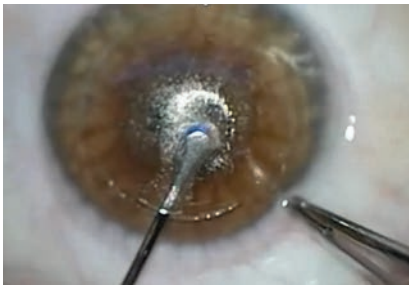
- ***Abnormal topography.*** An-

This article has no commercial sponsorship.

other aspect of the preop screening that comes into play is an abnormality in corneal topography. Though some surgeons might perform SMILE on a patient with abnormal inferior corneal steepening or subclinical asymmetry between the eyes that would rule out LASIK, I wouldn't. For a patient with borderline or suspect corneal topographies, I'll tell him that we're going to monitor him. Most of the time I'll ultimately perform surface ablation in such cases rather than risk performing a lamellar procedure like SMILE or LASIK. This is important because, based on certain demographics, the incidence of keratoconus may be higher than we expect.[1,2] In fact, a literature review of ectasia cases after SMILE that we performed found that most of them had subclinical keratoconus.[3] (An apparent increase in the disease's incidence may also be due to our use of more sensitive instruments and keratoconus indices, such as the Pentacam and the Galilei.)

• ***Ocular-surface concerns.*** If I encounter someone with very good corneal topography/tomography who would be a good LASIK candidate, the one thing that might make me shy away from LASIK and lean toward SMILE would be if she had a more noticeable dryness component in her eyes. So, if the patient has inferior staining or some signs of corneal fluorescent staining in the inferior aspect of her cornea, I'll do my best to bring this under control with our punctal plugs, Restasis/Xiidra or other anti-inflammatory agents over a period of three to six months. However, if she still has signs of dryness even after this therapy, I'll tend to favor SMILE over LASIK.

This approach is just based on my personal experience. Some studies have shown that SMILE can cause less dryness than LASIK[4,5] while at least one study found no appreciable difference between the two in terms of ocular surface disease measurements.[6]

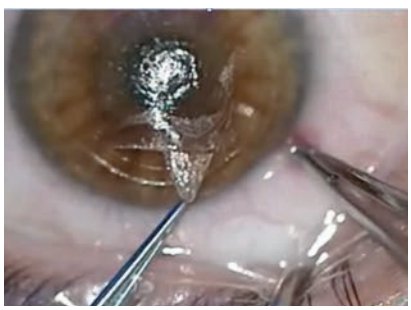


Sweeping too quickly and forcefully with the dissector can tear the lenticule.

However, I've observed that when I perform LASIK on patients with dry eye, there's a lot more corneal decompensation postop when compared to SMILE. These LASIK patients with preop dry eye will usually develop a lot more superficial punctate keratopathy in the inferior aspect of the cornea, perhaps due to more corneal nerve dissection.

• ***The ratio of astigmatism to myopia.*** If a patient's refractive error has components of both myopia and astigmatism, and the astigmatic component is 40 percent or more of the refractive error, I prefer to do LASIK in such a patient, if possible. On the other hand, if the proportion of astigmatism is lower, for instance, 1 or 1.5 D, and the myopic component is a higher percentage at -6 or -7 D, I would lean toward SMILE.

This is because I feel our LASIK nomograms are more fine-tuned than our SMILE nomograms. It's my impression that, so far, even with the nomogram adjustments I have for SMILE, I have to increase the level of myopic correction. For example, if someone is a -7 D myope, I sometimes have to add 7 to 12 percent to the spherical component of the correction. For astigmatism, on the other hand, I don't have to increase the amount at all; I just go by the measured power of the astigmatism. I'm hoping that, with time, we'll have more refined nomograms for SMILE, similar in reliability to LASIK's.



After removing the lenticule, be sure to check for any remnants left behind.

As a subset of this, the overall amount of correction matters too. If you're just starting, it's better if you perform it on a patient with a higher level of correction because his lenticule will be thicker and, therefore, easier to work with. Once you've done about 50 cases, you can start doing low corrections, such as -1.5 D and less.

Procedure Pointers

Once you're sure that SMILE is right for a particular patient, there are steps you can take during surgery to make sure you achieve the best outcomes possible.

• ***Docking the laser/creating the lenticule.*** Since the Visumax is a femtosecond laser, it needs to be docked using a suction ring in order to perform its photodisruption. The key is to have a picture of the patient's tomography or topography when you're sitting at the operating table, so you can see where the angle kappa and fixation point are with respect to the center of the pupil. When you're docking the laser, the laser is getting closer to the eye, and the patient is looking at the light, you'll notice that the line of sight might be aligned with the pupil's center. However, if you have that preop topography/tomography to refer to, it can help you with proper alignment.

I also encourage surgeons to keep the corneal surface moist, but not too moist. If it's too moist, it will create too large of a meniscus between the applanation glass and the patient's epithelium. You also don't want to dock

too slowly or too quickly, in order to avoid distorting the corneal surface. Doing this will ensure that you have a good anterior and posterior dissection. When you're massaging the cap with a moist Weck-Cel sponge, the motion is actually the opposite of LASIK's: Start at 6 o'clock and brush toward the incision at 12 o'clock.

One challenge with SMILE that we don't have with LASIK is that the femtosecond laser has no iris registration or ability to compensate for cyclotorsion. When a LASIK patient lies supine, with the excimer laser you can actually rotate the ablation based on the patient's cyclotorsion or iris registration data. With SMILE, though, since you manually mark the eye before the patient lies down and align the laser for the astigmatism correction, I think there's enough "noise" in the process that you can't distinguish 5 degrees of cyclotorsion in your actual attempted correction. So, with SMILE, when you're doing an astigmatism correction of 2 D on someone with an axis of 93, you really can't say that you won't be off by 7 to 10 degrees. Because of this, I feel that SMILE has more efficacy and predictability on lower astigmatic corrections than higher ones.

One of the most common complications surgeons will notice with SMILE is the loss of suction. Depending on when during the photodisruption this occurs, you may have to abort the procedure. If you've completed the posterior dissection and lose suction afterward, that's actually good—you can redock and restart the laser. However, if you lose suction during the posterior dissection, you have to abort. This is because it's the posterior cut that determines the power of the correction.

If you have to abort, you can convert the patient to a LASIK procedure immediately, creating a flap with the Visumax. Or, you can cancel the procedure, wait one to three months, and then bring the patient back to attempt SMILE again.

• ***The side incision.*** One thing to be aware of when you make the side incision is that you can potentially cause an epithelial defect. If this occurs, I advise surgeons to place a bandage contact lens on the surface to allow the epithelium to heal more smoothly at the incision. Doing this decreases the risk of epithelial ingrowth occurring.

• ***Dissecting the lenticule.*** Once the side incision is made, you use manual instruments to dissect the anterior aspect of the lenticule, then the posterior, before removing it. Of all the steps of SMILE, this is the one with the steepest learning curve.

First, visualization is important. Though the Visumax has a good microscope, at the moment, the only way to focus it is with a joystick. This poses problems because you also need your hands to perform the dissection. So, as you're trying to dissect the lenticule, if you lose focus, you have to stop and move your hand over to the joystick to refocus. In most other microscope platforms, however, the focus is controlled by a foot pedal, which allows the surgeon to keep both hands on the eye.

When dissecting, it's best to start with the anterior plane, then do the posterior. To dissect the anterior plane, use a sharper instrument, something a little longer than a Vanes scissors or Sinskey hook, to find the edge of the lenticule at the incision. The edge is usually inside the incision by a millimeter or so. Once you find the anterior edge of the lenticule with a sharp dissector, switch to a broad dissector and dissect it by a few millimeters with a gentle circular motion, followed by a slow advance of the instrument.

One mistake some surgeons make is that, as soon as they find the anterior plane, they'll intensely move the instrument back and forth, which can tear the lenticule, especially if the lenticule is for a low-power correction. Instead, gently use the broad dissector to advance the anterior plane toward the visual axis, and then below the visual axis. The movement should be slow enough not to tear the cap or torque the cornea too much. Once the anterior plane is dissected, repeat the steps for the posterior dissection.

In some cases, it can be difficult to differentiate the anterior and posterior planes, and you may accidentally dissect the posterior first. This isn't a disaster, but it does make things more challenging. If this happens, it can sometimes be easier to move to a surgical microscope to find the anterior plane and complete your dissection.

If you don't do a systematic dissection, you can sometimes end up with remnants of the lenticule. These can cause residual refractive error, so it pays to be thorough when dissecting.

• ***Postop regimen.*** In addition to a topical antibiotic, it's important to put these patients on topical steroids immediately, so on the first day, they take a steroid such as fluorometholone every hour. We continue the steroids for four weeks: q4h q.i.d for a week; t.i.d for a week; b.i.d for a week; then q.d. for the last week. This is necessary because we still see more inflammation than after LASIK, or than is seen by international SMILE surgeons who have access to better software.

Since these patients are on steroids for a longer time than LASIK patients, you have to monitor their intraocular pressure. It's possible for these patients to develop pressure-induced stromal keratopathy, in which interface fluid masks the true IOP. If you suspect PISK, take peripheral IOP measurements to make sure you're getting an accurate measurement. If it is PISK, discontinue the steroid and prescribe a glaucoma drug.[7]

Results and Complications

If you're thinking about performing SMILE, here's what to expect:

• ***Results.*** I'll speak about my experience first. In the very first set of

postop visits—hour one, hour six, 24 hours, and 48 hours—LASIK patients' vision is better than SMILE by about a line. However, by one month, and then six months, you really can't see a difference in terms of overall outcomes, efficacy or predictability if your SMILE nomogram is refined and you're using the most up-to-date energy and spot/line separation settings. Previously, SMILE patients saw about 20/20 or 20/30 in the first four or five days postop. Now, I'd estimate that most SMILE patients are 20/25 or better on the first day. In terms of contrast sensitivity and the scatter index, these measures continue to improve postop until they're equivalent to a postop LASIK by the third month.

In one prospective, randomized study, 70 patients were randomized to receive SMILE in one eye and LASIK in the other. The average refractive error was -5.3 ±1.8 D in the SMILE eye, and -5.2 ±1.7 D in the LASIK eye. At three months, 99 percent of SMILE eyes and 97 percent of LASIK eyes achieved SE within ±1 D of attempted correction (p=1.0), and the UDVA was 20/20 or better in 84 percent vs. 87 percent of SMILE and LASIK eyes, respectively (p=0.63). At 12 months, the researchers say that SMILE was similar to LASIK in terms of efficacy (85 percent vs. 83 percent UDVA ≥20/20; p=0.81), predictability (99 percent vs. 99 percent within ±1 D of attempted correction SE; p=1.0) and safety.[8] At our practice, we compared SMILE to the toric ICL and topography-guided LASIK and found that SMILE may be comparable to toric ICL for patients with high myopia or myopic astigmatism, but SMILE may have a longer visual recovery compared to TG-LASIK than previously indicated.[9]

• ***Complications.*** As mentioned earlier, the most common complication a surgeon will encounter is suction loss during the procedure. There's also a risk of abrasions at the incision or wound gape due to excessive manipulation. For the former, as noted earlier a bandage contact lens will help prevent epithelial ingrowth. If the wound is gaping, try to approximate the edges of the incision together and then place a bandage contact lens.

A group of surgeons listed their complications after 1,500 SMILE procedures. The most common complications they found were grade 0.5 to 1 haze (7 percent), a dry ocular surface on day one (4.2 percent) and epithelial islands at the incision (0.6 percent). Intraoperatively, there were abrasions at the incision (6 percent), lenticule extraction difficulty (1.8 percent), a minor tear at the incision (1.8 percent) and suction loss (0.7 percent).[10]

If we see inflammation in the interface, we treat it the same as in LASIK. First, we try to control it with steroids. If that's not enough, we use systemic steroids. Finally, we wash the interface, though we haven't had to do that yet.

• ***Enhancements.*** Though not necessarily a "complication," an enhancement isn't desirable either. Roughly 3 percent of SMILE patients will need an enhancement.[11]

Currently, the simplest way to perform an enhancement is to do PRK. However, if you want to get creative, the Visumax can convert the SMILE cap to a LASIK flap, and it can create a thinner flap using the existing cap. In the end, though, a PRK is probably best at this point. However, I don't recommend using mitomycin-C with these enhancements.[12]

Table 1. Visual Outcomes after SMILE in Recent Studies (≥ 50 eyes)

Author	# eyes	Preop SE	Postop SE	% seeing 20/20 uncorrected postop
Blum 2020*	56	-4.79 D	-0.35 D	59%
Lin 2014**	60	-5.13 D	-0.09 D	85%
Hjortdal 2012***	670	-7.19 D	-0.25 D	61%

**Blum M, Lauer A, Kunert K, et al. 10-Year Results of small incision lenticule extraction. J Refract Surg 2019;35:10:618-623.*
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In conclusion, I've found SMILE to be a useful addition to my suite of surgical procedures. In the right patients, and using the proper technique, SMILE can provide good outcomes for your patients, as well. REVIEW

Dr. Moshirfar is the director of clinical research at the Hoopes Vision Research Center in Draper, Utah, and adjunct professor at the Moran Eye Center. He is also co-director of the Utah Lions Eye Bank in Murray, Utah. He has no financial interest in any of the products mentioned.

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A Mix-and-Match Comeback?

Christine Leonard, Associate Editor

Some surgeons are rediscovering that a blended IOL approach may be a good option for increasing a patient's range of vision.

Though multifocal IOLs are designed to work bilaterally to take advantage of binocular summation, many surgeons have had success mixing and matching different multifocal IOLs to increase the patient's range of functional vision. Proponents say that mixing and matching complementary multifocals enables surgeons to take advantage of both IOLs' best features while potentially minimizing common visual side effects such as glare, halo, reduced contrast sensitivity and reduced visual acuity in the intermediate and near ranges.

"Mix and match opens a range of different possibilities for treating patients with different visual expectations and different eye characteristics, such as subtle irregular corneas and large pupil sizes," says César Vilar, MD, a cataract surgeon, medical researcher and medical director of the Hospital de Olhos Francisco Vilar in Teresina, Brazil.

Recently, the method has received new attention since good visual acuity at the intermediate range is more important than ever for computer and other technology-related tasks like reading on a tablet, and because more patients are demanding spectacle independence. In this article, cataract surgeons share their experience with the mix-and-match method and offer tips for choosing the best IOL combinations.

Mix and Match Beginnings

"Back when there were only monofocal intraocular lenses, inducing monovision (targeting plano in the dominant eye and a myopic target, such as -1.5 D or -2 D, in the non-dominant eye) was very common," Dr. Vilar explains. "However, many patients complained about the lack of stereopsis.

"When the high-add bifocal intraocular lenses, such as the Alcon ReSTOR +4 D and the Tecnis ReZoom, were initially introduced, a large number of patients reported dissatisfaction due to poor quality of vision—mainly because of dysphotopsias," he continues. "This discouraged many surgeons from implanting those lenses. The same thing happened with pseudo-accommodating lenses, because of the loss of function after capsule fibrosis. When low-add diffractive and EDOF lenses such as the ReSTOR +2.5 D and the Tecnis Symfony were introduced, surgeons promptly adopted these lenses and abandoned the high adds because patients reported fewer complaints. As a result, mix and match fell out of use.

"However, the low-add lenses didn't

provide enough near vision without the aid of spectacles for some patients," he says. "This prompted surgeons to try placing a low-add EDOF in the dominant eye and a high-add EDOF in the non-dominant eye. This strategy delivered good to excellent results, and grew increasingly popular among surgeons."

Kendall Donaldson, MD, MS, professor of clinical ophthalmology and medical director of Bascom Palmer Eye Institute at Plantation in Plantation, Florida, says we're fortunate to have such a large range of lens options in 2020. "This allows us to customize cataract surgery to achieve the very best results for our patients," she says. "Most lens manufacturers offer a variety of options providing various focal points and optical profiles."

Complementary Combinations

"Surgeons around the world have differing opinions with regard to mixing and matching," says Dr. Donaldson. "I think this is evidence that despite having achieved wonderful advances in the world of IOL technology, we still have no perfect lens that provides all focal points with optimal quality of vision and without side effects. There's always a compromise between range and quality of vision."

Dr. Vilar says that typical mix and match combinations used today include the Tecnis Symfony or the Tecnis multifocal ZKB00 (+2.75 D) in the dominant eye and the Tecnis ZMB00 (+4 D) or ZLB00 (+3.25 D) in the non-dominant eye; as well as the Zeiss AT LARA (an EDOF) in the dominant eye and a multifocal Zeiss AT LISA in the non-dominant eye (neither of which is approved in the United States). "You might also use the ReSTOR SN6AD1 (+3 D) in the non-dominant eye and the ReSTOR SV25T0 (+2.5 D)," he adds.

"Each lens manufacturer has generated a family of lenses with various focal points and optical profiles that work well together," says Dr. Donaldson. "One excellent example of this synergy is the Johnson & Johnson family of lenses. I'll often place a Synergy lens (EDOF) or Tecnis +2.75 D multifocal lens in the first eye and then evaluate the patient's function and perception postoperatively. If the patient is 100-percent thrilled with the outcome, I'll place the same lens in the second eye. However, if the patient wants more near vision, I may choose to increase the reading power with a Tecnis +3.25 D multifocal lens. Fortunately, these lenses are very complementary, and patients appreciate the increased range of vision at near distances when combining them.

"Typically, it's advised to place the lens with less add power in the dominant eye since most uncomfortable photic phenomena happen for distance vision, and these lenses are better tolerated."
— César Vilar, MD

"Similarly, Alcon has developed a family of ReSTOR lenses (+2.5 and +3 D) which also work very well together," she says. For example, a ReSTOR +2.5 D in the dominant eye for good distance vision complements a ReSTOR +3 D in the nondominant eye for near vision. According to Dr. Donaldson, this combination can give a patient more freedom from reading glasses.

Since Alcon released its PanOptix lens last year, Dr. Donaldson says many surgeons who were using the Alcon ReSTOR lenses (+2.5 and +3 D) have switched to matched PanOptix lenses. "The PanOptix lens offers a broader range of vision when compared with the Alcon ReSTOR lenses, since it provides clear vision at three focal points: distance; intermediate; and near," Dr. Donaldson says. "Since the release of this lens, I find that I'm matching lenses with a plano target more frequently within the Alcon platform. I think this is evidence that the technology has continued to improve. More patients are achieving good-quality vision with a broader range of vision, hence patients choose to proceed with the same lens that was placed in the first eye."

Combinations to Avoid

When mixing and matching different multifocal lenses, both Dr. Donaldson and Dr. Vilar emphasize the need to avoid creating a troubling level of anisometropia. One of the main critiques of the mix and match method is just that—that mixing different multifocal IOLs will result in patients comparing their eyes.

According to Dr. Donaldson, there's more of a tendency for patients to become preoccupied with comparing the optical differences of each IOL when you mix different brands or lens families, such as a diffractive lens with a refractive lens. "I find that mixing and matching is most successful when lenses are mixed within the same family (manufacturer) because the optics are similar," she notes. "Additionally, you should stick with one color of lens. Of note, Alcon lenses come in both clear and yellow (blue-blocking

César Vilar, MD

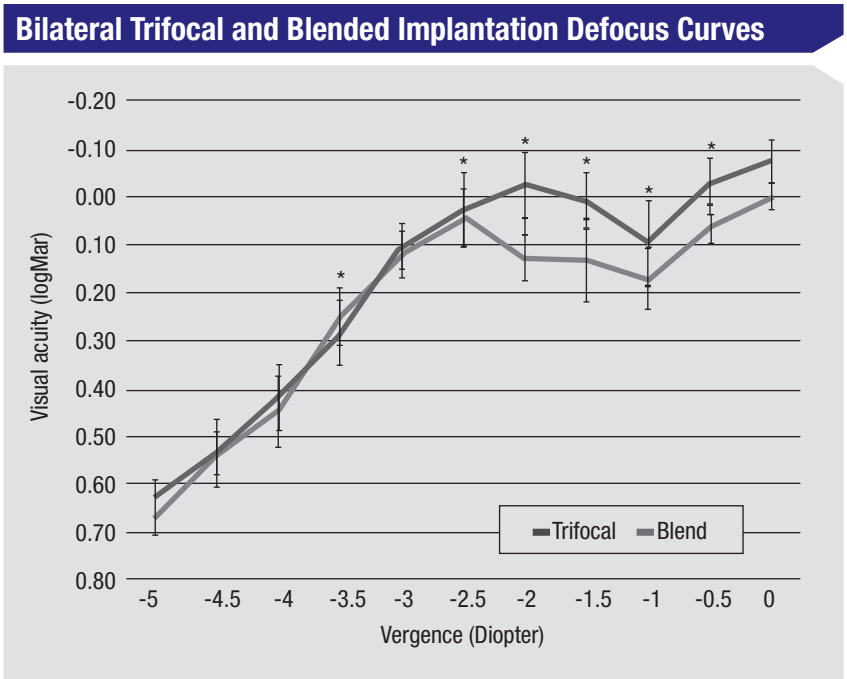

Figure 1. Binocular distance-corrected defocus curves for trifocal and blended (ReSTOR +2.5 D and +3 D) implantation groups.[5] While both groups exhibited a trifocal pattern, the trifocal group demonstrated statistically significantly better visual acuity from -2 D to plano and at -3.5 D ($p<0.05$), as indicated by the asterisks.

chromophore) versions."

Bilateral vs. Mixed

"When compared to bilateral implantation of multifocal intraocular lenses, the mix-and-match method has been demonstrated to be superior in some respects by a number of studies," says Dr. Vilar. He says the blended approach can increase a patient's functional range of near vision. An Alcon study comparing 53 bilateral implantations of a +2.5-D multifocal and 50 blended implantations of a +2.5 and +3-D multifocal found both groups had similar visual results. The blended group had better, but not statistically significantly better, near visual acuity.[1]

Compared to bilateral implantation of trifocal intraocular lenses, research has shown that both lens modalities produce good visual outcomes. The first reported comparison of multifocal mix-and-match implantation and bilateral trifocal implantation compared the AT LISA trifocal for bilateral implantation (n=25) and the ReSTOR for blended implantation (an intermediate add in the dominant eye and a near add in the nondominant eye) (n=30). It found that both methods provided good visual outcomes.[2] (One of the researchers received a study grant from Alcon for the paper.) Both groups demonstrated excellent binocular near and distance vision, good visual function and similar low rates of dysphotopsias. The trifocal group had significantly better intermediate visual acuity from 2 m to 67 cm, corresponding to grocery shelves and car dashboards, and both groups had comparable visual acuity at distances from 60 cm to 40 cm, corresponding to computer or reading distance.

A prospective, nonrandomized, consecutive study comparing bilateral implantation of the PanOptix with blended implantation of the Tecnis Symfony and Tecnis ZMB00 multifocal included 40 eyes of 20 patients. Both groups achieved good acuity for distance, intermediate and near vision. The researchers say that the blended implantation group was superior for very near distances and for intermediate and long distances greater than or equal to -1.5 D of vergence. The bilateral trifocal group had superior uncorrected intermediate visual acuity at 60 cm and uncorrected near visual acuity at 40 cm.[3]

One purported advantage of the mix-and-match method is its ability to reduce unwanted photic phenomena through the use of complementary lenses. In a nonrandomized comparative study in Japan,[4] researchers compared the visual outcomes of patients implanted bilaterally with a trifocal IOL and patients implanted with multifocals with a different near add in each eye (+3 D and +4 D). They found that the bilateral trifocal group demonstrated better distance and intermediate vision than the blended group ($p\leq0.0325$), but both groups had comparable near visual acuity. While the trifocal group had significantly better contrast visual acuity and stereoacuity than the blended group, the incidence of halo symptoms tended to be worse in the trifocal group.

"Our group in Brasilia from CEORA published studies comparing the two different strategies," says Dr. Vilar. "We analyzed VA outcomes, defocus curves and contrast sensitivity in 20 patients for either mix-and-match (ReSTOR +2.5 D and ReSTOR +3 D) or trifocal implantation in both eyes, and achieved similar results in both groups."[5] The study found that average preoperative CDVA was better in the blended group than in the trifocal group (0.15 versus 0.24 logMAR, Snellen: 20/28 versus 20/35; $p=0.073$), though the difference was not statistically significant. Defocus

curves in both groups exhibited a trifocal pattern, but the trifocal demonstrated statistically significantly better visual acuity from -2 D to plano and at -3.5 D (*Figure 1*). Overall, the trifocal performed better and showed excellent visual acuity through a large interval of vergence (-0.1 and +0.1 logMAR [Snellen: 20/15 and 20/25] from -2.5 D to plano). Dr. Vilar says this suggests that bilateral trifocal implantation may have better tolerance of a hyperopic residual refractive error when compared to blended implantation.

Studies that employed questionnaires asking about subjective quality of vision didn't find consistent differences between groups using mix-and-match approaches and groups that received bilateral implantation of trifocal lenses.[6]

Dr. Donaldson says that she's found EDOF and diffractive multifocals work well together. "We did a study on mixing and matching EDOF lenses with the Tecnis +3.25 D a couple of years ago," she says. (Her group presented its findings at ASCRS 2019 with Johnson & Johnson Vision.)[7] "We found that the patients who received the mixed-and-matched IOLs had the highest degree of spectacle freedom and the lowest degree of side effects, such as glare and halos. The technologies were complementary."

Lens Selection Variables

There are several important objective variables that the discerning cataract surgeon must take into consideration when selecting the appropriate lenses for a mix-and-match combination. Some of those include a measurement of the patient's preferred reading distance, which can be used to adjust the IOL's near focal point, corneal topography and pupil size.

"Corneal topography and pupil size in different light conditions are important factors," explains Dr. Vilar. "Some corneas may have subtle irregularities that would at first contraindicate a high-add implant. However, a low-add or EDOF IOL may be suitable in these eyes. Then, placing the high add in the other eye would reduce the chance of photic phenomena. Patients with large pupils in mesopic conditions may experience worse dysphotopsias, especially at night and while driving. Similarly, the low-add or EDOF IOL in the dominant eye may reduce the chance of dissatisfaction."

Some surgeons believe that eyes with corneal irregularities, such as those that have undergone previous refractive surgery, may fare better with a zero-aberration IOL, such as the enVista (Bausch + Lomb), which can compensate for some levels of IOL decentration.

Dr. Vilar cautions surgeons to remain aware of eye dominance when selecting lenses. "Eye dominance is a subjective test," he says. "It often changes after the surgery, which may exacerbate photic phenomena if the high-add lens ends up in the dominant eye. Also, because each eye is set for a different near focus, some activities for near vision, such as reading for extended periods of time, may be more difficult. Typically, it's advised to place the lens with less add power in the dominant eye since most uncomfortable photic phenomena happen for distance vision, and these lenses are better tolerated."

Patient Counseling

The other equally important aspect of lens selection is a subjective one. Dr. Vilar says he believes the key to success with presbyopia-correcting lenses is the surgeon's ability to clearly explain to patients what they should expect from their vision after surgery.

"I usually reserve the mix-and-match approach for patients who demand high visual quality, those who often drive at night and those who insist on a high level of spectacle independence," he says. "I explain to patients that there's no guarantee that they'll have no photic phenomena, but they're likely to be tolerable. Additionally, I tell patients they may need spectacles for activities with near vision such as reading for long periods. If they accept these drawbacks, I go the blended implantation route."

Dr. Donaldson agrees that a thorough explanation of visual expectations is important, but she also recognizes that this isn't an easy task. "We could sit with patients all day long and go through every lens option, but we don't really have time to do that and the patient isn't equipped with the full knowledge base to make the decision," she says. "As surgeons, it's our job determine the patient's visual needs and expectations for cataract surgery. We can then use this knowledge to make the best lens choice for our patients. I always explain to patients that cataract surgery is a process involving two eyes, so we do the first eye and evaluate the results and use that information to make any adjustments and modifications for lens choice in the second eye.

"I never tell patients an outcome will be 100 percent, but I do tell them we're trying to give them the best range of vision possible and freedom from glasses," she continues. "Some patients may still need light reading glasses for very small print. But if they're 100-percent free of glasses, they're extra happy. We try to underpromise and over-deliver."

In addition to educating the patient on their lens options and what to expect, it's important to listen to and learn about him or her. Dr. Donaldson says that "learning about our patients' lifestyles, occupations and pastimes allows us to best assess their visual needs so that we can combine

lenses to meet our patients' expectations for cataract surgery."

Dr. Donaldson says that those who are looking for the highest degree of spectacle independence, more range of vision or want the possibility of altering second lens choice are good candidates for receiving different, complementary multifocal lenses.

She adds that patients who may not be the best candidates for the mix-and-match approach include those who can't spend the extra money for multifocals; those who like wearing their glasses or aren't interested in spectacle freedom; and those who say they won't tolerate any degree of halo or glare from a multifocal lens. "Some patients might know family members who were extremely happy with their refractive surgery, but sometimes you'll have a patient come in whose family member or friend had a bad experience, and they're afraid of that technology," she says. "These experiences may also affect how satisfied your patient is."

Making Compromises

"Fortunately, the evolution of IOL development has provided us greater functionality with decreased side effects such as glare and halos," says Dr. Donaldson. "However, despite these advances and numerous multifocal and EDOF lens options, we still often need to combine lens options to achieve patient satisfaction. The original mix-and-match combination—mini monovision with standard IOLs—is still the number-one way we allow patients to have more spectacle independence after cataract surgery. Patients achieve high levels of satisfaction with this combination." REVIEW

Dr. Donaldson discloses financial relationships with Alcon, Johnson & Johnson and Bausch + Lomb. Dr. Vilar receives lecture fees from Alcon.

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(Continued from page 29)

practice conducted a one-year study (referenced earlier). Two prototypes of phaco choppers were used, including a sharp tip for chopping and a blunt tip for providing a scaffold while they performed phacoemulsification. The purpose of the study was to evaluate the efficacy of the chopper scaffold technique as a means to reduce to reduce endothelial cell damage and postop corneal edema when removing hard cataracts.

The randomized, prospective study involved 35 eyes of 30 patients who underwent phacoemulsification between July 2018 and June 2019. Inclusion criteria permitted the use of eyes with nuclear sclerosis grade >4 and an anterior chamber depth >2 mm. Central corneal thickness and endothelial cell count constituted the studied parameters.

Alcon's Centurion phacoemulsification system was used for the surgery, employing a balanced tip and power at 75 percent in the longitudinal mode, vacuum set at 650 mmHg and an aspiration flow rate of 42 cc/minute for the chopping maneuvers.

After the chopping maneuvers, individual fragments were mobilized out of the bag and emulsified at the pupillary plane, using 90-percent power in torsional mode with 600 mmHg of vacuum and an aspiration flow rate of 50 cc/min.

Study Results

Following their year-long study, the surgeons tabulated the findings and found that the mean endothelial cell loss after three months was about 6 percent, which was within normal limits, decreasing from 2,246.2 ±193.55 preop to 2,106.77 ±185.54 postop. All of the postop eyes had clear corneas on the first postop day. The mean central corneal thickness increased to about 6 percent of its preop thickness the day after surgery (rising from 527.93 ±22.09 µm to 560.43 ±23.22 µm) but this measurement dipped to the preop values at the end of day seven.

In conclusion, the surgeons believe they have established a simple technique that can be adapted by their peers. "Quite simply, it can help preserve the corneal endothelium better," says Dr. Tushya Om Parkash. "Along with power modulations and modified nuclear disassembly techniques, this approach will help surgeons make phacoemulsification in rock hard cataracts much safer." REVIEW

Doctors Tushya OM Parkash, Rohit Om Parkash and Mahajan report no relevant financial disclosures.

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After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Best regards,
Kendall Donaldson, MD, Yousuf Khalifa, MD, Mitchell Weikert, MD, MS

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Glaucoma: When Visual Fields & OCT Disagree

Christopher Kent, Senior Editor

Conflicting data is a common occurence. Surgeons offer their advice on how to proceed.

Today, surgeons managing glaucoma rely largely on optical coherence tomography (which measures ocular structure) and visual fields (which assess function) to detect disease and monitor progression. However, disagreement between them is a frequent occurrence. That raises the question of what to do when a disagreement arises.

Disagreement between OCT and visual field data can happen for a number of reasons, ranging from the nonlinear relationship between changes in structure and function as glaucoma progresses, to artifacts in measurements, to nonglaucomatous pathologies and anomalous optic discs. Here, surgeons with expertise in this area discuss some of the reasons OCT and visual field data may disagree when assessing glaucoma, and what you can do when it happens.

Structure Vs. Function

"Disagreement between structure and function measurements in glaucoma is very common," notes David S. Greenfield, MD, a professor and Douglas R. Anderson Chair in Ophthalmology, vice-chair for academic affairs and co-director of the Glaucoma Service at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. "Our group analyzed data from 147 glaucomatous eyes that were followed annually for six years with serial visual field testing and OCT measurements of the retinal nerve fiber layer and macula.[1] Only 7 percent of these eyes showed consistent progression in all three parameters."

Certainly one of the most common reasons for a disagreement between OCT and visual fields is the best-known one: Measurable changes in structure don't always parallel measurable changes in function. "As biological changes associated with glaucoma progression occur, ganglion cell axons die and eventually become atrophic," notes Dr. Greenfield. "Longitudinal changes in retinal nerve fiber layer and macular ganglion cell thickness should [in theory] agree with serial changes in visual function using standard automated perimetry, yet many patients with glaucoma progression develop isolated changes in structural tests without detectable changes in visual function, and vice versa."

"There are definitely times when one measurement shows signs of worsening while the other seems stable," agrees Philip P. Chen, MD, a professor and Grace Hill Chair in the department of ophthalmology at the University of Washington and chief

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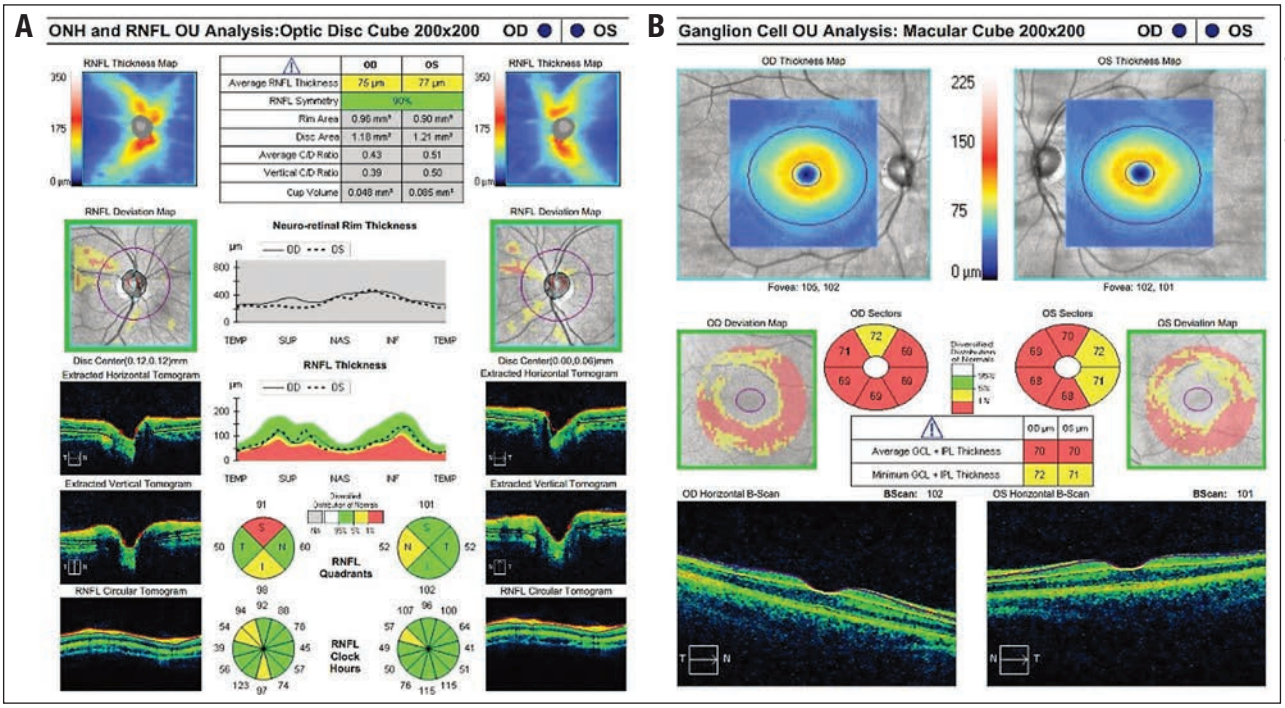


All images courtesy of Joel S. Schuman, MD, FACS

Glaucomatous damage in highly myopic patients may cause abnormal measurements that can be confused with glaucomatous damage. Above: A) Thin superior and inferior RNFL OD and thin nasal RNFL OS; and B) diffuse bilateral thin GCIPL, both caused by myopia.

of ophthalmology at the UW Medicine Eye Institute. "For example, in early glaucoma the visual field often continues to look fine, but OCT may indicate that structural change is taking place. Harry Quigley's lab showed many years ago that it took a 20-percent loss of ganglion cells to produce a 5-dB loss detectable on automated perimetry.[2]

"If the OCT suggests structural change in early disease," he adds, "I'd get a confirmatory OCT and then explain to the patient that although we can't detect any symptoms yet, starting to treat is the smart thing to do."

Joel S. Schuman, MD, FACS, director of the NYU Langone Eye Center, and Elaine Langone Professor and chairman of ophthalmology and professor of neuroscience and physiology at NYU Langone Health, NYU Grossman School of Medicine, points out that the same disconnect applies when disease is advanced, although in the opposite direction. "If a more advanced glaucoma patient has a very thin nerve fiber layer, let's say below 55 µm, you'll typically have both an abnormal visual field and abnormal OCT," he says. "However, if you're following for progression, the mean OCT nerve fiber layer thickness may not be changing, even though the patient is actually getting worse. That's because of the OCT floor effect. Meanwhile, the visual field can still show progression because it has more dynamic range remaining at the low end."

"The OCT RNFL measurement may lose its usefulness sooner than visual field testing does," agrees Dr. Chen. "Because of glial scar tissue or other nonfunctional structural tissue in the retinal nerve fiber layer, the measurable thinning stops—even though damage is continuing. As a result, OCT RNFL thickness may reach a measurement floor, while areas on the visual field are still followable, especially if you're using a 10-degree test rather than a 24- or 30-degree test."

Other Reasons for Disagreement

Conflicting data can arise for other reasons as well. These can be loosely grouped into three categories: technology-related issues; ocular-structure-related issues; and pathology-related issues. They include:

• ***Different testing strategies.*** "For example, regions of retinal topography may not directly correspond to the same regions in visual field testing," Dr. Greenfield explains.

• ***Poor OCT scan quality.*** Dr. Schuman points out that it's essential to have good-quality testing, particularly with OCT. "If the scan quality isn't good enough, the device won't be able to properly segment the layers of the retina," he says. "That's a big cause of what Richard Lee, MD, likes to call 'red disease.' Improper segmentation causes a false reading of a thin nerve fiber layer, and it shows up on the report as red."

• ***The visual field learning effect.*** "This can have a big impact," notes

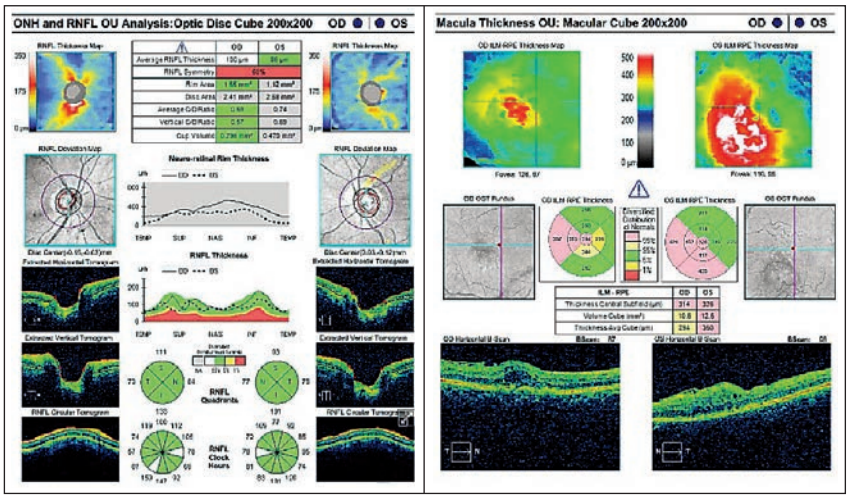
Christopher A. Girkin, MD, chairman of the Department of Ophthalmology and Vision Sciences at Callahan Eye Hospital, University of Alabama. "It's not uncommon to get a few points and even clusters that can mimic a real visual deficit and cause a structure-function disparity."

Eyes that aren't average can also cause misleading readings:

• ***Very thick or thin nerve fiber layer***. Dr. Schuman notes that conflicting visual field and OCT data can happen when the nerve fiber layer is very thick or thin, even with good-quality testing. "Suppose the patient has a relatively thick nerve fiber layer, but it's below the normal range," he says. "Approximately 75 µm of nerve fiber layer thickness is what we call the tipping point. If the mean nerve fiber layer thickness is greater than that amount, even though an area on the OCT may show up as being abnormal—and it may really be abnormal—it's unlikely that you'll find an abnormality in the visual field. This can also be true over time; if you're following a patient with a nerve fiber layer thicker than 75 µm, OCT progression analysis may detect progression as the NFL thins, while the visual field remains normal. It's more unusual to get conflicting data when the nerve fiber layer thickness falls in the intermediate zone."

• ***Variability in the optic nerve head.*** Dr. Girkin points out that normal variability in the optic nerve head can cause glaucomatous readings. "Larger optic nerve heads can appear abnormal on scans," he notes. "A tilted disc, in particular, can look abnormal when it's really just anomalous."

He points out that the appearance of the optic nerve on visual examination can be misleading as well. "Probably the most common cause of non-artifactual pseudo-structure-function disparity—in the presence of real disease—is the glaucomatous microdisc," he says. "In an optic nerve head with a small neural canal, even a small degree of cupping can represent significant injury that can be missed if the impact of the scleral canal size on the appearance of the nerve isn't appreciated."



Actual RNFL thinning can be masked by macular edema, which thickens the RNFL, potentially confounding glaucoma assessment.

Nonglaucomatous pathology can also cause a disagreement between OCT and visual fields:

• ***High myopia.*** "In a myope—especially a high myope—the retina has to cover a lot more area than in an emmetropic eye," Dr. Schuman explains. "That results in a thinner retina overall. As a result, someone with moderate to high myopia may have a nerve fiber layer or macular measure that's thinner than the normal thickness range, despite the retina being normal. That abnormal measurement may be perfectly normal for them.

"Unfortunately, the normative OCT databases don't include people with highly myopic eyes," he explains. "In general, the people included in those databases only have up to -6 D of myopia—if that much. So a high myope may show up as abnormal on an OCT but produce a normal visual field. You may be left wondering whether or not that patient really has glaucoma."

• ***Macular degeneration or edema.*** "You have to be careful about interpreting OCT measurements when the patient has macular degeneration or macular edema," Dr. Schuman notes. "Moderate to advanced macular degeneration can cause retinal thinning. On the other hand, macular edema can make the nerve fiber layer measure thicker than it otherwise would be, so you have to be careful with that interpretation as well. Such a patient may have an abnormal visual field that reflects true thinning of the nerve fiber layer, but you can't measure it with the OCT because the tissue has been thickened with fluid."

• ***Non-glaucomatous optic neuropathy.*** Dr. Girkin says this is another important—and potentially life-threatening—cause of structural and functional disparity. "Compressive lesions, retrobulbar optic neuritis, ischemic optic neuropathy and other lesions that affect the visual pathways can all cause visual field defects that defy the typical structural and functional relationship seen in glaucoma," he says.

Resolving the Discrepancy

What should clinicians do when assessing discordance between structure and function? Some options involve using the technology differently to seek clarification; other options

involve looking for explanations that involve the eye or nonglaucomatous pathology. In terms of using the technology differently, ophthalmologists offer these suggestions:

• ***Repeat the testing.*** "This is the first thing to do, particularly in eyes with poor-quality imaging or unreliable visual fields," Dr. Greenfield says.

• ***Look at the raw OCT data.*** "Probably the most common cause of discrepancy between OCT and visual fields is an artifact in either the structural or functional test," says Dr. Girkin. "On the imaging side, edge-detection artifacts are very common, as well as artifacts associated with epiretinal membranes and other structural abnormalities unrelated to glaucoma. So, if you encounter a discrepancy between OCT and visual field, scan the visual field for artifacts. Look at the raw, cross-sectional B-scans from the OCT. That's very important because you can't rely on the interpreted OCT data—the color printouts. Many OCT scans have edge-detection errors, so unless you look at the raw data, you're not going to know whether the anomaly is an artifact."

"Poor-quality data and measurement variability will often lead to discordance between structural and functional measurements," agrees Dr. Greenfield. "OCT measurement artifacts exist in up to 30 percent of scans; they often result from eye movement, shadowing associated with ptosis or eyelid blink, or algorithm failure."

• ***Focus on the macula.*** "The idea of targeted structure and/or functional analysis makes a lot of sense," says Dr. Girkin. "It's been known for a while that macular damage can occur early and can progress, but I think that fact is appreciated a lot more today. Looking at the macula, or specific segments of the nerve that are prone to damage, is very important."

"You can rely on the macula to show change late in the disease," notes Dr. Chen. "The macula has large reserves of ganglion cells, so it's one of the first areas to show damage in early disease, and it's one of the last areas in which you can follow damage in advanced disease. It's useful at every stage, although it may be harder to use it for this purpose in early disease, because the changes will be fairly subtle."

As noted, macular edema can also cause misleading OCT measurements. "If there's any doubt about whether or not edema is present," says Dr. Schuman, "a macular scan will often reveal it."

• ***Look for localized areas of change.*** Dr. Schuman notes that if progression is occurring, you may be able to find specific local areas changing on the OCT. "That's especially easy with the progression analysis that's available on the Zeiss Cirrus OCT device," he says. "If you don't have that option, but you're able to look at the volumetric scan for areas of statistically significant change, you may be able to see small areas that show up as thinning."

• ***Increase the visual field stimulus size.*** "One way to improve your ability to measure change when disease is advanced is to concentrate on 10-degree visual fields while increasing the stimulus size," notes Dr. Chen. "A standard visual field is done with a size-III stimulus, which has a surface area of 4 mm^2. But when you approach the point at which the patient can't detect those stimuli any longer, resulting in a totally black visual field, you can switch to a size-V stimulus, which is 64 mm^2. This can allow the patient to detect the stimulus again, despite advanced glaucomatous damage, giving you more useful data to follow over time.

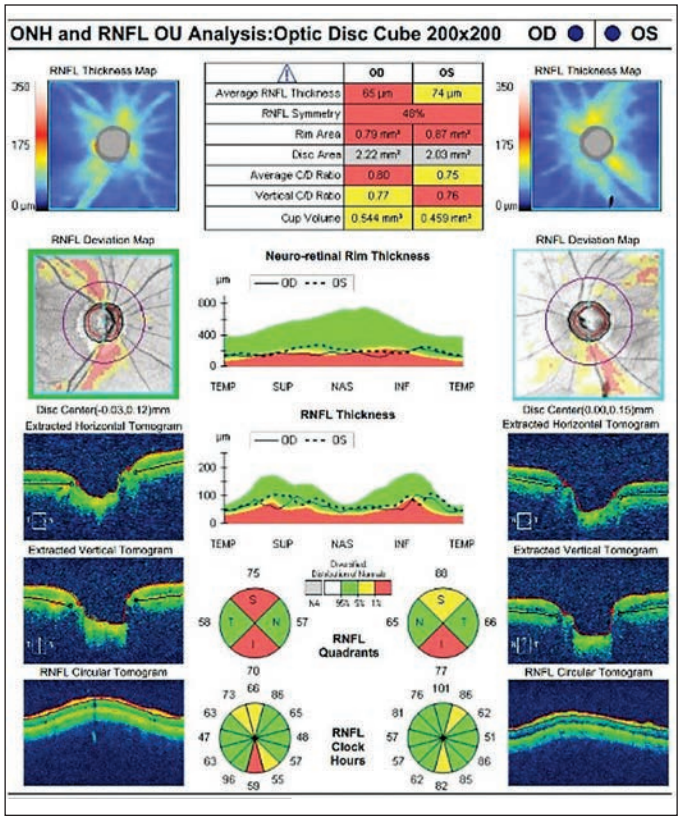
"Of course," he adds, "once you switch to a different stimulus, you won't be able to compare the results to earlier tests. You'll have to get a new baseline, but then you can follow the change over time again. Unfortunately, some test algorithms—for example, SITA-standard, -fast, and

-faster—are not available with all stimulus sizes."

• ***Use optic disc photos.*** Dr. Chen says that when pathology causes OCT scans to be unreliable he sometimes turns to optic disc photography to get a better idea about the patient's condition. "Sometimes I still use a stereo photograph as a final arbiter," he says. "At our academic medical center, we have ready access to stereo fundus photography. When seeing a new patient I get a baseline OCT, but at the next visit I'll get a stereo fundus disc photo to have that baseline as well.

"One reason disc photos are often valuable is that they're sort of an obsolescence-proof technology," he notes. "OCT technology advances all the time; I won't be surprised if I'm using a different OCT in five years than I'm using today. That means it's entirely possible that my current OCT data will be unreadable by the newer machines, and that makes old-school disc photos very valuable."

Dr. Schuman points out, however, that most ophthalmologists today rarely take disc photos. "Part of that has to do with subjective vs. objective interpretation, and part of it has to do with the difficulty of getting simultaneous stereo disc photos," he says. "To a large extent, clinicians today rely more on OCT data. However, there's still value in a disc photo, especially when a patient has difficulty cooperating during the physical exam. You can look at a snapshot for as long as you like, whereas if the patient's eyes are darting around during the exam, evaluating the disc will be a challenge. I'd have a very low threshold for taking a photo in that situation."



One way to confirm that OCT progression is real is to look at the location of the damage. Above: OCT reveals bilateral thin inferior-temporal RNFL, thin superior-temporal RNFL OD, and borderline RNFL OS. These are common areas for glaucomatous damage.

Taking the Eye Into Account

As noted earlier, structural abnormalities and pathology can result in visual field-OCT disagreements.

• ***If the patient is a high myope… .*** Dr. Schuman says deciding whether a high myope really does have glaucoma often comes down to the doctor's experience. "The ophthalmologist's expert knowledge and experience play a significant role in this situation," he says. "You need to consider all of the relevant factors, including risk factors, IOP, the appearance of the optic nerve, and so forth. The decision-making process is a little bit more difficult. Here, OCT technology is more useful for longitudinal follow-up than for the initial exam."

When you're doing an initial exam on a high myope, Dr. Schuman notes that the location of the thinning documented on the scan can be helpful. "If you look carefully at the optic nerve head scan, you may see more thin nerve fiber layer nasal to the major bundles of the RNFL," he says. "That can be a clue that the thinness is the result of myopia, not glaucoma. But you have to be very careful in moderate to high myopes when deciding whether the OCT findings are real, especially when they disagree with the visual field. Sometimes, even in myopes who don't have glaucoma, you can find an arcuate defect in the nerve fiber layer and an abnormality on the visual field that looks like glaucoma. It can be an artifact of the myopia and perhaps an abnormal insertion of the optic nerve."

• ***Look for disc hemorrhages.*** "Clinicians should carefully examine the optic nerve for disc hemorrhages, a useful biomarker of progression," says Dr. Greenfield. "OCT imaging can't detect them."

"A physical examination of the fundus can tell you things the OCT can't—especially with regard to color," agrees Dr. Schuman. "You can't see a disc hemorrhage on OCT. There are OCTs like the Topcon device that give you a fundus photo in addition to the OCT, but most of the other OCTs have infrared or scanning laser ophthalmoscopic images, or they use the *en face* OCT as the fundus image. As a result,

you can miss details, especially with regard to color, that you would see if you looked at the fundus during the physical exam. I think a visual inspection of the retina is very important."

"You still have to rely on your clinical exam to detect hemorrhages," says Dr. Chen. "I'm pretty compulsive about checking for them, so I'd like to think I don't miss too many. But sometimes they're very small and hard to detect, and patients' pupils are not dilated at most visits. In addition, clinicians are dealing with pressure to maintain speed and efficiency in patient throughput. It's theoretically possible to identify a hemorrhage on an infrared OCT scan, but in most cases you'd probably miss it."

Dr. Greenfield notes that optic disc photography may be more sensitive for detecting disc hemorrhage than clinical examination. "In the Ocular Hypertension Treatment Study," he says, "optic disc hemorrhage was a strong predictor of progression and was more frequently identified by review of optic nerve photographs (75 percent) than by clinical examination (10 percent)."[3]

"It's definitely easier to identify hemorrhages on a stereo photograph," agrees Dr. Chen. "The problem, of course, is that patients don't get photographed at every visit. For all of these reasons, if there's one part of the exam you really need to spend time on, it's looking at the disc and checking for hemorrhages. Of course, if you can, review a photo at your leisure after clinic."

• ***Look for paracentral defects associated with acquired pits.*** Dr. Girkin says this is one sign that should cause you to look closely at the central visual field. "These are very common in our tertiary referral clinic," he notes. "Whether it's an inferior notch, or a superior notch with a pit with some beta-zone atrophy around it, this type of lesion is generally associated with central loss.

"Targeted focused imaging of the macula in those cases is really helpful, even if the patient's fields are full, because you might miss a central defect," he says. "I also get a 10-2 visual field when the eye has pits, if there's injury within the macular vulnerability zone, if there's a defect that's primarily paracentral on the 24-2 visual field, and in advanced cases when the patient has dense constriction."

• ***Check for non-glaucomatous optic neuropathy.*** Dr. Girkin points out a number of things that can be used clinically to decide whether a discrepancy between OCT and visual field indicates the presence of a nonglaucomatous optic neuropathy. "Probably most important on that list are color vision and central acuity," he says. "Glaucoma generally attacks side vision, at least as detected in conventional testing. While it can cause some macular damage, it generally doesn't affect color vision and acuity until very late in the disease.

"On the other hand, conditions that affect the retrobulbar nerve tend to cause central damage and color vision loss very early on," he continues. "So color vision deficit and a drop in central visual acuity can be a big clue. When there's a disparity between OCT and visual fields in any glaucoma patient, it's important to check color vision—although I don't think many of us do. It's one of the key ways to differentiate nonglaucomatous neuropathy from glaucomatous neuropathy. If there's any question, make sure the cranial nerves are intact. Carefully evaluate for an afferent pupillary defect, and perform a complete neuro-ophthalmic assessment and history."

Confirming OCT Data

OCT data can be challenging to interpret. Dr. Schuman offers these suggestions:

"There are a couple of things to look at that would convince me that

what I'm seeing in an OCT scan is real," he says. "One is the location of the progression. Is the thinning located in an area such as the superior or inferior temporal part of the nerve fiber layer where it exits the optic nerve, an area I would expect to be getting thinner in glaucoma? If so, that suggests the thinning is real. If your device can give you a volumetric scan, the shape of the thinning area can be another clue. If it's expanding out from the optic nerve head toward the macula in an arcuate pattern, that also suggests that the thinning is real.

"A third way to look for supporting evidence that a change is real is to do a macular scan in addition to the optic nerve head scan," he continues. "You should see thinning in the macula that corresponds to the thinning in the nerve fiber layer. Actually, I always scan both the optic nerve head and the macula, partly as a way to make sure my findings are real. Of course, you won't get reimbursed for doing two scans; one of them has to be gratis. But I think the information I'm able to get, and the increase in certainty with which I'm able to make a decision, makes it more than worthwhile.

"A fourth strategy is to look for enlargement of the cup-disc ratio," he says. "If that cupping enlargement is occurring in the setting of thinning nerve fiber layer and thinning macular parameters like the ganglion cell complex or the ganglion cell inner plexiform layer, that's internal corroboration that the measurements on the OCT are real, even in the absence of visual field changes.

"Finally, it's worth looking carefully at the visual field again," he says. "Often there are subtle visual field abnormalities or changes that, in the absence of these OCT measures, you might not consider to represent real change. If they match the changes in the OCT spatially, that's corroboration that what the OCT is measuring is real. All of these strategies can be helpful when you're trying to decide whether to treat the patient."

However, Dr. Schuman adds an important caveat. "The threshold for making the decision to treat should be based on what the next treatment step is," he says. "Your threshold should be higher if your next treatment step is the OR than if the next treatment step is adding a medication or doing laser trabeculoplasty."

What about OCTA?

One of the latest iterations of optical coherence tomography is OCT angiography, which can reveal the functioning vasculature in parts of the retina. Could this help determine whether glaucomatous disease or progression is present when the OCT and visual field data disagree?

"OCT angiography has the potential to detect glaucoma progression," notes Dr. Greenfield. "OCTA can measure vessel density with high repeatability and reproducibility. Studies have shown that capillary density measurements with OCTA are well-correlated with structure and function, and may be useful across a wide spectrum of disease severity."

"Many of us are hoping that OCTA may be able to show that vascular changes occur before structural changes like retinal nerve fiber layer thinning, ganglion cell inner plexiform layer thinning and optic disc hemorrhages," notes Dr. Chen. "If that turns out to be true, this technology might allow us to detect glaucoma and glaucoma progression even earlier than we can today using changes in the retinal nerve fiber layer or ganglion cells. Some longitudinal data supporting this has been published, but more studies are needed."

"I think OCT angiography is very promising, in terms of what it might predict," says Dr. Girkin. "It's good for looking at the superficial and deep retinal vasculature. However, the critical vasculature that's damaged in glaucoma is likely the intrascleral branches of the short posterior ciliary artery that feed the lamina cribrosa. I suspect that the defects seen in OCT angiography are just related to a loss of ganglion cells that, in and of itself, probably doesn't cause glaucoma, although causality remains elusive."

Dr. Girkin adds that the technology is very sensitive to background "noise." "The whole idea behind OCTA is that it uses that noise to determine motion, so even a slight change in the signal-noise ratio can have a pretty significant effect on the OCTA scans," he points out. "Despite these caveats, OCTA is showing great promise. But so far, I don't think we fully understand how to use it in routine clinical practice."

Dr. Schuman agrees. "A number of papers suggest that OCTA in the lab can provide additional information about eyes with glaucoma, but I'd say that in terms of clinical utility we're probably not there yet," he says. "We haven't figured out how best to use that technology to detect disease or progression in glaucoma, but several groups, including our own, are working on this." REVIEW

Dr. Girkin has received research support from Heidelberg Engineering in the past. Dr. Schuman is a consultant for Zeiss. Dr. Chen has consulted for Allergan in the past. Dr. Greenfield reports no relevant financial disclosures.

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Regenerative Medicine In Ophthalmology

Michelle Stephenson, Contributing Editor

Revolutionary therapies are being evaluated for their ability to treat a variety of conditions, from AMD to congenital degenerations.

A number of companies are exploring regenerative medicine as a means for treating eye disease. "This is certainly in its infancy, but we are starting to see good results," says David S. Boyer, MD, who is in practice in Los Angeles. "Delivery devices for stem cells have improved dramatically, which will pave the way for more stem cell utilization."

Chicago's Jennifer I. Lim, MD, adds that CRISPR-Cas technology will allow physicians to edit out the abnormal gene and insert the normal one. "I think we will have regenerative medicine to restore what has been depleted by atrophy or genetically programmed degeneration," she says. "We will have ways to prevent the atrophy by giving a trophic factor to regenerate what's still capable of growing, and then we'll have ways to use stem cells to repopulate tissues and gene therapy to inject material to correct the problem that would cause degeneration again further down the road."

Gene Therapy

Several companies are working on gene therapies for retinal diseases, trying to follow in the footsteps of Spark Therapeutics and its therapy Luxturna.

• ***Luxturna (Spark Therapeutics).*** Luxturna is the first FDA-approved gene therapy for a genetic disease. It is a one-time prescription gene therapy product that can be used for patients with an inherited retinal disease caused by mutations in both copies of the RPE65 gene and who have enough remaining cells in the retina.

It was approved by the FDA in 2017 for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss. According to the FDA, the primary evidence of Luxturna was based on a Phase III study that included 31 participants and measured the change from baseline to one year in a patient's ability to navigate an obstacle course at various light levels.[1] Patients who received Luxturna demonstrated significant improvements in their ability to complete the course at low light levels compared with control patients.

• ***Intravitreal Gene Therapy (ADVM-022, Adverum).*** Adverum is investigating ADVM-022 as a one-time intravitreal injection for the treatment of wet AMD.

"Adverum has a modified AAV2 vector, which can be injected in the vitreous, and the results have been very encouraging," says Pravin U. Dugel, MD, who is in practice in Sun City, Arizona. "Obviously, the big advantage is that it can be injected into the vitreous. It's being studied for neovascular

macular degeneration, and the results recently have shown that the number of injections is dramatically less in patients who otherwise would need repeated injections."

In the spring of 2020, Adverum presented interim data from cohorts 1 to 3 of the OPTIC Phase I trial of ADVM-022. They reported that all six patients in cohort 1 were rescue-injection-free after a year. Eight of 11 patients treated with a lower dose have also been rescue-injection free. The company says that ADVM-022 has been safe and well-tolerated, with no dose-limiting toxicities, and inflammation has been manageable with topical steroids; 69 percent of treatment-related adverse events are mild and 31 percent are moderate. In April, researchers dosed the first patient in Cohort 4 of the trial.[2]

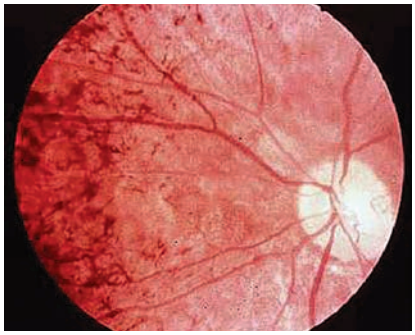
In late May, the company initiated the INFINITY trial, evaluating the treatment in diabetic macular edema.

• ***Sepofarsen (ProQR).*** Sepofarsen, designated QR-110, is an RNA-based therapy, delivered via intravitreal injection, for congenital retinal diseases. The therapy is currently undergoing a Phase II/III trial called Illuminate, in which it's being used to treat Leber's congenital amaurosis type 10.

In the study, there was a high percentage of cataract development (eight out of 11 cases, 73 percent; six required surgery). There were two cases of mild cystoid macular edema that were treated successfully, and two cases of subclinical retinal thinning. However, pooled dose group data showed a significant improvement in the treatment group vs. baseline in best-corrected acuity, full-field stimulus threshold test and in the patients' performance on a mobility course.[3]

Sepofarsen has an orphan drug designation, and received fast-track designation and rare pediatric disease designation from the FDA.

• ***RGX-314 (RegenxBio).*** RGX-314 is being developed by RegenxBio as a novel, one-time subretinal treatment that includes the NAV AAV8 vector containing a gene encoding for a monoclonal antibody fragment. It has the potential to treat conditions such as wet age-related macular degeneration and diabetic retinopathy. The expressed protein is designed to neutralize VEGF activity.



Retinitis pigmentosa is a target of many gene and stem cell therapies under investigation.

The company has an ongoing Phase I/IIa trial of RGX-314, which includes 42 patients with severe wet AMD that requires frequent anti-VEGF injections. These patients have been treated across five dose cohorts, with doses ranging from 3 x 10^9 GC/eye to 2.5 x 10^{11} GC/eye.

At two years, RegenxBio reports that RGX-314 continues to be well-tolerated across all cohorts, with no drug-related serious adverse events reported. It says that cohort 3 has shown a mean (14-letter) improvement in vision and stable retinal thicknesses. Half of the patients (three out of six) have remained anti-VEGF-injection-free, and 67 percent (four out of six) are injection-free from nine months to two years. In cohort 5, 73 percent of the patients (eight out of 11) have been injection-free for nine months.[4]

"The impressive thing about the RegenxBio data is that it's not just that the number of injections are also dramatically less, but, for the first time, we're able to see that there's a dose-dependent increase in the amount of protein that's produced, which we've never seen before," Dr. Dugel says. "So, that is very impressive. Additionally, RegenxBio has a partnership with Clearside. Researchers believe that transfection of the vector can be as efficient given by suprachoroidal injection as subretinal delivery. This is very significant because the delivery may now be converted from a surgical procedure delivered in the subretinal space to a clinical procedure injected in the suprachoroidal space."

• ***HMR59 (Hemera).*** CD59 is a protective protein that is normally found on the plasma membrane of cells, and it protects cells from a natural inflammatory cascade in the body called complement that acts as a part of the body's nonspecific immune response. It is believed that macular degeneration is caused by an overactivity of complement. Studies have shown that patients with AMD have less CD59 present in the retina to protect their cells from damage caused by complement. Currently, Hemera's gene therapy (HMR59) is under FDA-approved Phase I clinical testing for the treatment of both wet and dry AMD. When HMR59 is injected in the eye, it increases the ability of retina cells to make a soluble form of CD59 called sCD59. According to the company, the soluble CD59 circulates within the retina to block complement from further damaging the retina.

• ***OCU400 (Ocugen).*** Another gene therapy for retinitis pigmentosa, but at an earlier stage of development (Phase I), is Ocugen's OCU400 (AAV-NR2E3). According to the company, OCU400 consists of a functional copy of a nuclear hormone receptor gene that's delivered to certain cells in the retina using a viral vector.

Stem Cell Therapy

The idea behind stem cell therapy is to use implanted stem cells, which have the potential to develop into different types of useful cells, to generate healthy cells to replace those lost

in retinal conditions. Here's a look at what's in the pipeline:

• ***jCyte.*** jCyte's developmental stem cell therapy to treat retinitis pigmentosa is currently undergoing Phase IIb trials. Researchers at jCyte found that retinal progenitor cells could rescue and even replace diseased retinal cells, so they developed jCell, an allogeneic human retinal progenitor cell suspension. Patients will receive a single intravitreal injection, which can be done in the office. Early results from the Phase IIb trial have shown that the treatment is safe and doesn't trigger an immune response.

"The advantage here is that it's a clinic procedure as opposed to a surgical procedure, and it can be repeated," Dr. Dugel says. "So, the fact that it's not as invasive and is repeatable is a plus. Additionally, this treatment is agnostic of the retinitis pigmentosa subtype." The company recently entered into a licensing agreement with Santen.

• ***hRPC Stem Cell Therapy (ReNeuron).*** ReNeuron is using proprietary human retinal progenitor cells, which, when transplanted onto the retina, have the potential to preserve existing photoreceptors and potentially reduce or halt further deterioration of vision.

The company has announced positive long-term data from its ongoing Phase I/IIa clinical trial of its hRPC stem cell therapy for the treatment of retinitis pigmentosa.

Patients in the study had a successful surgical procedure with sustained clinically relevant improvements in visual acuity compared with baseline, ReNeuron says. Additionally, the company says that long-term efficacy data from the study continue to show a meaningful clinical effect from the therapy out to 12 months.

The company has submitted a protocol amendment to the Phase IIa trial to treat an additional nine patients.

• ***ASP7317 (Astellas).*** Astellas is using cell therapies to address vision loss. ASP7317 is an investigational therapy derived from pluripotent human stem cells, and it is undergoing a clinical trial for the treatment of dry AMD. The company is sponsoring a two-stage, multicenter clinical trial to evaluate the optimal dose, safety, and efficacy of ASP7317.

• ***CPCB-RPE1 (Regenerative Patch Technologies).*** Regenerative Patch Technologies is developing cell-based implant technology for the treatment of retinal diseases. CPCB-RPE1 is a bioengineered implant consisting of stem cell-derived, mature, polarized retinal pigment epithelial cells in a single layer on an ultrathin synthetic parylene membrane. It is designed to replace the retinal pigment epithelium and Bruch's membrane.

The membrane is implanted into the subretinal space during an outpatient surgical procedure. Preliminary results from a Phase I/IIa clinical trial demonstrated the safety of the implant.

Several assessments of visual function were also conducted. After CPCB-RPE1 implantation, patients demonstrated improved ability to focus or fixate on a target using the diseased area of the retina, and patients showed either stable or improved visual acuity, with one patient demonstrating a 17-letter improvement.

"This is a patch with an artificial membrane-type surface where the cells are very elegantly transplanted exactly where they're missing," Dr. Dugel explains.

CRISPR

Researchers are still in the early stages of assessing the genetic manipulation technique known as CRISPR (clustered regularly interspaced short palindromic repeats) for eye disease. It's a new kind of genetic engineering that allows scientists to edit DNA. While traditional gene therapy uses viruses to insert new genes into cells in an attempt to treat diseases, CRISPR directly makes changes in DNA. The technique uses targeted molecular tools that work like scissors to cut out abnormal DNA and replace it with normal genetic material.[5]

Editas Medicine and Allergan are conducting a human trial of a CRISPR gene-editing therapy for inherited blindness. The Phase I/II trial will test a single subretinal injection of AGN-151587, also called EDIT-101, in 18 patients with Leber's.[6]

Researchers plan to administer low, medium and high doses of the drug in children, and medium and high doses in teens. Similar to Luxturna, EDIT-101 is delivered to retinal cells via an adeno-associated virus.

Dr. Boyer says that CRISPR seems promising. "The most important thing about CRISPR is that you can take diseases that are hereditary and remove the gene," he says, "so that the person who is affected can't pass it along. However, we are messing with Mother Nature, so we don't know what the long-term effects will be. Certainly, if you have a one-gene or two-gene disease, you may be able to modify enough to be able to overcome the defect. This is very exciting technology." REVIEW

Dr. Boyer is a consultant to Allergan, jCyte, Adverum and RegenxBio. In terms of products mentioned in the article, Dr. Dugel is a consultant to Allergan, Santen and Spark Therapeutics. Dr. Lim has a financial interest in Santen.

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Fixing a Wayward Trabeculectomy Bleb

Bleb failure is fairly common over time, but a number of techniques can help you return many blebs to functionality.

Martha M. Wright, MD, Minneapolis

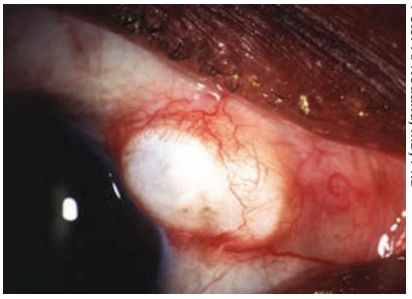
Many trabeculectomies fail over time, even if the surgery itself goes perfectly. That's true for a number of reasons, including that patients heal differently; they may or may not use their postop drops or follow up as instructed; or they may have a preexisting condition that influences the final result. (Ideally, you've taken these factors into account when choosing your procedure.)

When a trabeculectomy does begin to fail, it's usually the result of scarring. Because scarring is a gradual process, a sudden trabeculectomy failure is unusual; it's more common to have trabeculectomy function decrease slowly over time. How long a trabeculectomy remains viable varies widely; some trabeculectomies don't fail during the patient's lifetime. A few of my patients have had a working trabeculectomy for more than 20 years—although those patients are in the minority.

The reality is that most patients who need a trabeculectomy are elderly. The prevalence of glaucoma increases in older patients, especially among those older than 80. For that reason, a trabeculectomy that works well for five to 15 years may be sufficient to prevent significant vision loss in these patients for the rest of their lives. Younger patients tend to heal better than older patients, increasing the likelihood of trabeculectomy failure, which may necessitate consideration of treatment options other than trabeculectomy for those patients.

Of course, failing to lower pressure enough isn't the only thing that can go wrong with a trabeculectomy. Trabeculectomy blebs can leak, which is dangerous because of the risk of infection. A leak can also cause hypotony maculopathy and blurred vision. Furthermore, blebs can sometimes expand across the globe in ways that irritate the patient's eye or cause a cosmetic problem. To put this another way, some trabeculectomy problems make the doctor unhappy; other problems make the patient unhappy.

Here, I'd like to discuss some common problems that can arise following a trabeculectomy and the options for addressing them. First, I'll discuss the issues that are disappointing to the doctor; then I'll talk about issues that bother the patient.



Peter A. Netland, MD, PhD

If an encapsulated bleb forms soon after surgery, putting the patient back on drops briefly may allow it to resolve. If an encapsulated bleb occurs more than a month or two after surgery, needling will probably be more effective.

When a Bleb Scars Down

When a bleb has become less effective, that usually means that the conjunctiva and supporting tissues have scarred down to the sclera. This occurs in one of two ways: either as generalized scarring that leaves the bleb looking fairly flat, or presenting as a dome-like bulge, often referred to as an encapsulated bleb or "Tenon's cyst." Either type of scarring results in poor pressure control. A large, diffuse bleb without significant scarring is much more likely to successfully

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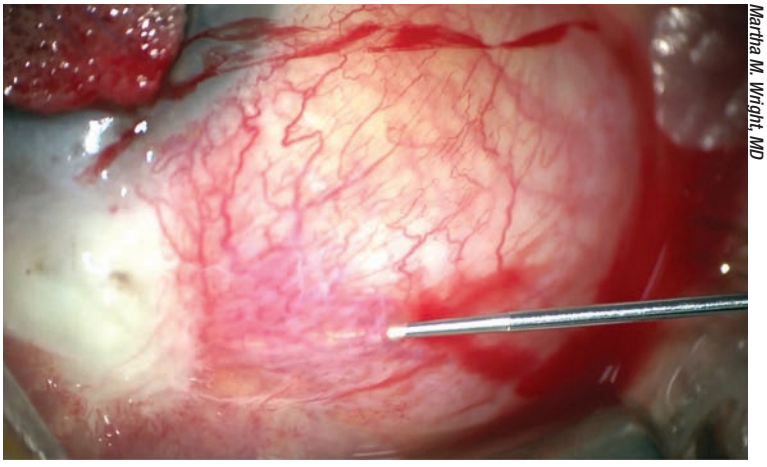
lower IOP.

Generally, when a bleb has become less functional because of scarring, we have several options: Add topical medications; perform a different glaucoma procedure; try to release some of the adhesions using needling; or perform a surgical revision. There are several ways to needle or revise a bleb—which means there are problems with every method and no one "best" way. Prevailing opinions about the efficacy of needling seem to differ from practice to practice. Some doctors do a lot of needling to try to restore bleb functionality if the scarring isn't too serious, while others do almost none.



Martha M. Wright, MD

Needling a bleb to release scar tissue blockage can be done using a needle or an MVR blade (shown above). Although not every surgeon favors needling to rescue a bleb, it has the advantage that it can often be done in the clinic.

Needling has one big advantage over surgical revision: In some cases it can be done in the clinic. Whether or not you choose to needle a bleb in the clinic is partly a matter of personal preference and partly an issue of patient cooperation. If needling is going to be relatively quick and the patient is very cooperative, you may be able to do it at the slit lamp. If it's more involved, or you have concerns about how well the patient will be able to hold still, you may choose to do it in the OR. However, once you plan to perform needling or a surgical revision in the OR, it's worth considering whether this is the best use of resources. It might make more sense, in selected cases, to do a completely different procedure such as a tube shunt surgery that could have a higher rate of success.

Needling is usually done with one of two tools: a bent needle or a blade such as the MVR. Bending the needle to a 45-degree angle makes it possible to ergonomically reach over an obstacle such as the patient's brow. (Of course, if you're coming in from the temporal side, it's fine to leave the needle unbent.) The needle bevel allows you to use it like a blade. However, the sharp area of the tip is small and the shaft of the needle is flexible, making it hard to cut through thick scar tissue effectively. For that reason, when the needle is used, the surgeon often pokes a series of perforations through the scar tissue and then moves the needle side-to-side to "connect the dots." The resistance to cutting through the scar tissue may cause the eye to move around a fair amount when breaking through the scar tissue.

Unlike a needle, the MVR blade has a longer sharp edge and is more rigid, making it easier to cut or saw through scar tissue. (You can watch a video of this technique at the American Academy of Ophthalmology's website: aao.org/basic-skills/bleb-needling-failed.) I don't bend the MVR blade, so I tend to use it in the OR where I have more control over the position of the eye.

Generally, needling is directed at the area you believe is restricting the flow of aqueous. The needle may be directed subconjunctivally, beneath the scleral flap, or through the sclerostomy. Some surgeons have even developed an *ab interno* approach for needling, in which a 23-gauge needle enters the anterior chamber across from the trabeculectomy, is passed across the anterior chamber and out the sclerostomy, with the tip of the needle at the posterior lip of the scleral flap.[1]

If the needling procedure isn't done in the first week or two after surgery, it may be worthwhile to add an antifibrotic, either mitomycin-C or 5-FU, to help ensure that the scarring doesn't immediately resume. (In a published study comparing these two drugs as an adjunct to needling, mitomycin-C was shown to be to be more effective than 5-FU.[2])

Another option for a failing bleb is surgical revision.[3] This entails going back to the OR, applying mitomycin-C and revising the trabeculectomy to reestablish the flow. This usually means dissecting the conjunctiva again and cutting through some of the scar tissue that's impeding the flow of aqueous. The surgeon may or may not dissect the flap completely free. Unlike needling, where one does not have to close up or suture the entry site if it's some distance from the scleral flap, a surgical revision requires creating an incision, so you have to close it when you're finished.

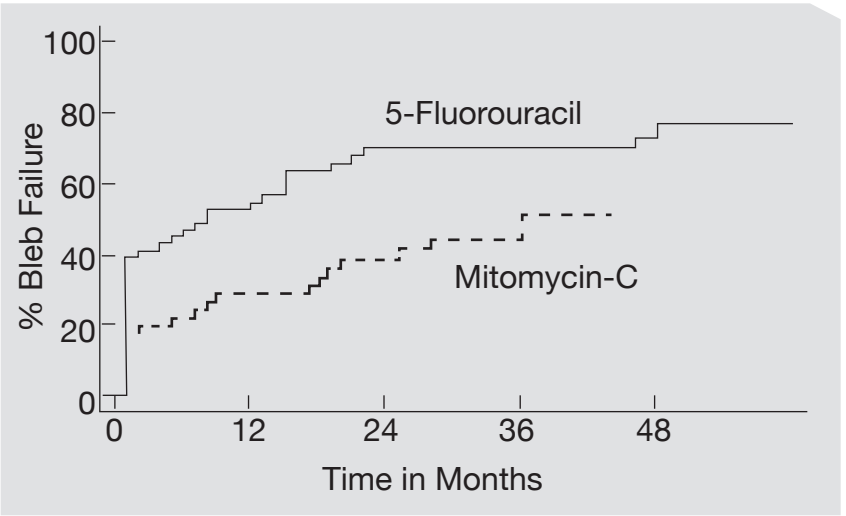
Managing Encapsulated Blebs

Some patients develop an encapsulated bleb early on following surgery. Unfortunately, studies have shown that pressure control isn't as good in trabeculectomy patients who have—or have had—an encapsulated bleb.

If an encapsulated bleb develops soon after surgery, it may resolve on its own, but many encapsulated blebs do not. Generally, when we do a trabeculectomy we don't want to put the patient on any glaucoma medications in the early postoperative period because the flow of fluid through the trabeculectomy site is essential to the functioning of the trabeculectomy. Suture lysis to increase flow and lower the pressure is usually preferred over adding medication after surgery, often in conjunction with digital massage. The one exception to this rule is when there's early encapsulation of the bleb. Laser suture lysis and digital massage may not be possible or effective in this scenario.

While some have recommended needling for early bleb encapsulations, studies have shown that in the first few weeks after surgery putting the patient back on drops may be more effective than needling. In many cases this will result in the bleb reverting to a more normal-looking trabeculectomy bleb. However, once you get more than a month or two from surgery, needling will probably be more effective than putting the patient back on drops. (Absent encapsulation, the strategy of needling to release scarred tissue is more effective when done soon after the surgery than when it's done years later, because the scar tissue will have become very well established at that point.)

Needle Revision With Mitomycin-C vs. 5-Fluorouracil



A 2009 retrospective study of 95 patients who received subconjunctival injections of MM-C (n=45) or 5-FU (n=53) before needling bleb revisions found that although there was no significant difference in complication rates between the groups, the likelihood of failure following the needling was lower with the use of MM-C.[2]

Managing a Bleb Leak

Bleb leaks are often associated with very thin bleb tissue, typically found in blebs that have a lot of scarring around them. The scarring makes the bleb smaller, and as blebs get smaller and more compressed the tissue tends to get thinner. This phenomenon has been likened to putting air into a balloon or surgical glove and then squeezing the air down into one tiny area; the balloon wall gets thinner and thinner. If a leak develops, the longer it leaks, the harder it is to close it up. As with trabeculectomies themselves, the flow of fluid keeps the hole open.

Bleb leaks are fairly common. That's especially true when an antifibrotic was used during the trabeculectomy, because the antifibrotic causes the bleb to have a thinner wall. Trabeculectomies performed with an antifibrotic also tend to continue to function longer, allowing more time for a leak to occur. It's possible that some leaks are intermittent, and therefore may be missed by the surgeon, but a persistent leak can lead to a bleb infection—or worse, endophthalmitis. So, when we discover a persistent leak, it's usually a good idea to try to repair it.

A persistent leak may be discovered in any of several ways. The patient may report a sudden increase in what they believe is tearing. They may wake up with a wet pillow, or report blurred or fluctuating vision. The surgeon may note that the patient's intraocular pressure is suddenly lower, or note a suspiciously thin area or a frank hole in the conjunctiva. Confirmation of a leak is done with Seidel testing.

There are many methods for trying to fix bleb leaks, but none of them is perfect. They include lowering the pressure by putting the patient on medication; patching the eye; or putting the patient on an eye drop that's a little irritating to encourage healing. Some clinicians may perform autologous blood injections into the bleb, and/or as a peri-bleb injection, which can be helpful in some cases. But in many cases you have to go back to the OR and do something surgically. The main thing is to not create a bigger problem than the one you're trying to fix.

Some of the most common surgical approaches involve pulling in healthier conjunctiva from the surrounding area to cover the leak, with or without removing the leaking tissue. Unfortunately, some eyes are so scarred that you can't move the surrounding conjunctiva—it's like concrete. In some patients, autologous conjunctival patch grafts can be

considered. Some surgeons have tried repairing a bleb leak by simply securing a piece of amniotic membrane on top of it, thinking that if the tissue remained there for a while it would heal the leak. Unfortunately, in practice that doesn't work very well.

My preference is to place an amniotic membrane under the conjunctiva. Rather than bringing healthier conjunctiva in, I lift up the patient's leaking conjunctiva, secure the amniotic membrane over the trabeculectomy site, put the conjunctiva back on top of the membrane and close the incision. The amniotic membrane tissue is a bit tedious to work with; it's kind of like manipulating a wet Kleenex. However, all procedures for fixing bleb leaks can be difficult, and I've had good success with this approach. I believe the amniotic membrane acts as a scaffold; the conjunctiva grows over it during the next week or so, healing the leak.

When the Patient is Unhappy

Occasionally, even after excellent pressure is achieved, changes in the bleb can make the patient unhappy. Most often this is because the bleb has expanded in size. A large bleb can be uncomfortable and/or produce unwanted cosmetic changes.

Sometimes a bleb extends down onto the cornea, slowly expanding toward the visual axis. In addition to making the patient uncomfortable, this can interfere with vision. The bleb is white and translucent (*see examples, below*) and tends to produce some scar tissue, so you don't want it to get into the visual axis. It can also alter the appearance of the eye, causing people to ask the patient: "What's wrong with your eye?"

The good news is that you can gently scrape the bleb extension off the cornea using a spatula blade and amputate it at the limbus. The bleb on the cornea usually peels up back to the limbus once you get it started. Surprisingly, this generally doesn't cause the bleb to leak; you usually don't have to do any suturing. In most cases,

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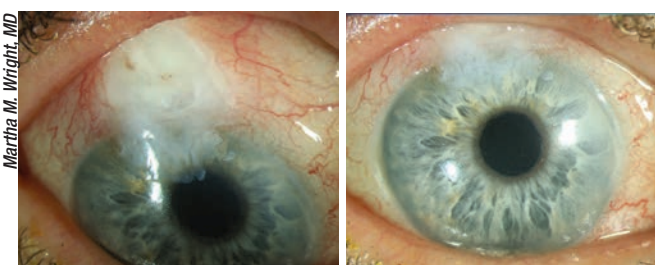
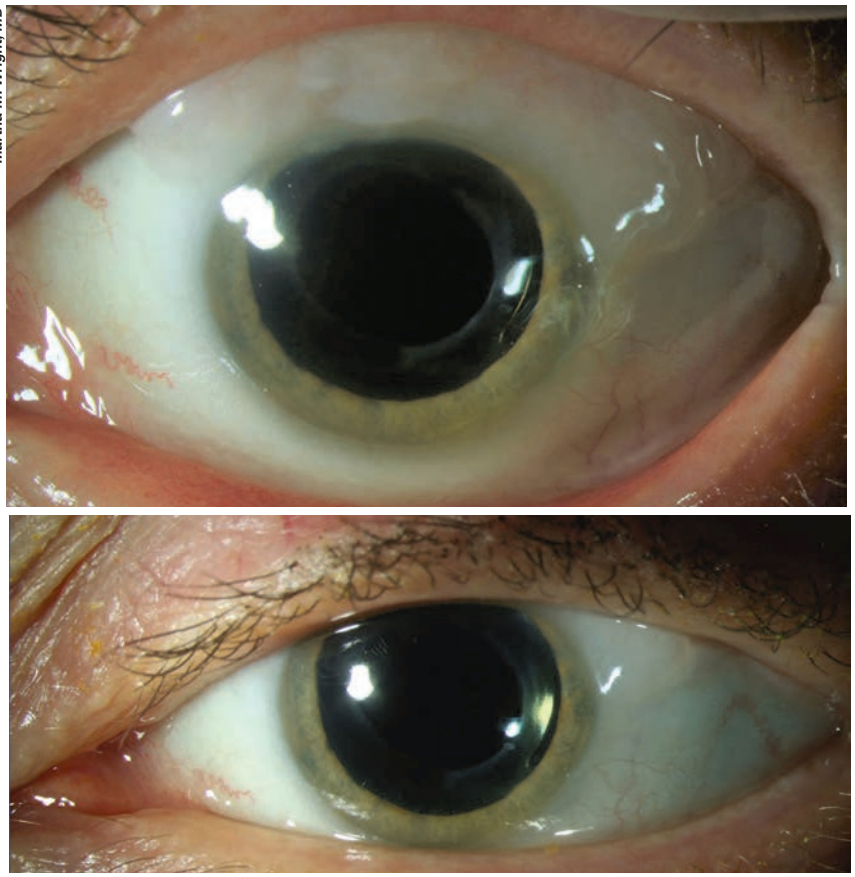


A large bleb may reach down onto the cornea, causing discomfort, cosmetic changes noticeable by others, and eventually interfering with vision. Usually, the bleb extension can be gently scraped off the cornea using a spatula blade, which usually doesn't cause a leak.

Martha M. Wright, MD



An exuberant bleb has been restricted by creating two lines of scarring that keep the bleb under the upper lid. With the lid in normal position, the bleb is now barely visible.

the cornea will re-epithelialize and the bleb won't start working its way back onto the cornea again—although sometimes it does, possibly requiring another excision.

If a bleb gets very large, it can cause bleb dysesthesia, making the eye uncomfortable—usually because it's interfering with the tear film. If the bleb protrudes, it can prevent the eyelid from moving over the eye in a smooth motion, and patients can feel it when they blink. Furthermore, a large bleb at the limbus can prevent the blinking reflex from spreading the tear film evenly over the cornea. This can create a dry spot, or dellen, resulting in a constant foreign body sensation that can be very uncomfortable. Some enlarged blebs cause a bubble to form on the edge of the lid, and the bubble pops every time the patient blinks. The patient can either feel the pop or hear it—or both! That's distracting, given the number of times a day we blink.

Occasionally, a bleb may simply expand all the way around the limbus, creating a bleb 360 degrees around the eye. Ironically, the IOP is usually excellent when this happens because a lot of aqueous is exiting the eye. Unfortunately, the large bleb may be uncomfortable and patients can be very unhappy if they feel the bleb every time they blink.

Often, these "exuberant blebs" will flatten out on their own given time—but not always. If it remains, you need to do something to make the patient more comfortable by limiting the extent of the bleb. In some instances, a laser re-shaping procedure (using a surgical marking pen as a chromophore for laser absorption) can lower the profile of the bleb, or reshape it. Some authors have recommended putting tight sutures over the lines you want to scar down; this would create enough scarring that the bleb should stay up under the eyelid and away from the palpebral fissure where it's most likely to be felt by the patient. You can reliably create two lines of scarring that will contain the bleb in a more limited area by making incisions through the conjunctiva down to bare sclera. (*See images, left.*)

I've done this procedure in the clinic at the slit lamp and in our treatment room, using a topical anesthetic, although you certainly could do it in the OR. Most patients who were miserable before this procedure have been very happy after a few days of healing.

Doing What Works

As we all know, trabeculectomy is not a perfect procedure, but it remains an important part of our treatment armamentarium. When we feel that a patient needs a trabeculectomy to prevent a loss of vision, strategies like those described here can help to restore a less than perfect bleb, allowing our patients to benefit from the lower pressure it provides. REVIEW

Dr. Wright is a professor in the department of ophthalmology and visual neurosciences at the University of Minnesota, and a glaucoma specialist at the Veterans Affairs Hospital in Minneapolis. She reports no financial ties to any product mentioned in this article.

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Oculoplastics Surgery and The Pandemic

Surgeons address the particular issues faced by oculoplastics specialists during practice shutdowns and gradual reopenings.

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COVID-19 is an unprecedented challenge that's brought providers in internal medicine, emergency medicine, anesthesia and critical care to the forefront. Specialists, amidst changes that include cancellations of clinic and procedures and adoption of telemedicine, are placed in the special position of weighing the tenets of public health against the needs of their unique patient populations. A field that epitomizes this is ophthalmology and, perhaps even more so, oculoplastics and orbital surgery. In this tumultuous time, we need to think critically about ensuring the best possible outcomes for our patients and for our practices, with a forward-focused approach. Here, we'll cover some areas of oculoplastics that have been affected by the pandemic, and how these areas can recover now that practices are beginning to reopen.

Minimizing Spread

As has been pointed out in the early days of the pandemic, ophthalmologists are at high risk of exposure to higher viral loads due to their proximity to the patient's face and contact with conjunctiva and tears, which can be sources of viral transmission.[1] Because of these risks, we've been compelled to minimize office staff to maximize patient safety, and many practices ensure that older physicians have a higher threshold for in-person interactions due to higher risk of COVID-19-related morbidity and mortality in older populations.[2] Aerosolizing procedures involving the sinuses and respiratory droplets, such as dacryocystorhinostomy, orbital fracture repair and orbital decompressions, as well as any operations that require general anesthesia and intubation, place oculoplastic surgeons at particularly high risk.[3] As part of the public health campaign against COVID-19, initial recommendations were to suspend elective procedures, identify high-risk patients and undertake urgent cases with heightened protections. Though some elective procedures are starting to be performed again, the latter two recommendations remain as important as ever.[4]

Specific Procedures

Our prime directive is to "first do no harm," but this becomes a challenging conundrum as we carefully reopen our country.

For example, many cancers of the head and neck extending to the orbit double in size within a few months.[5] Numerous studies have linked the extent of orbital involvement or metastasis of cancers directly to survival rates and other outcomes, necessitating prompt and urgent treatment.[6,7] As such, all orbital/periorbital lesions that are concerning for metastatic or aggressive malignancies, such as sebaceous cell carcinoma or melanoma, should be worked up and managed in a timely fashion.

A similarly thoughtful approach should follow for traumatic reconstructions. A large meta-analysis has recommended immediate reconstruction for specific findings, including diplopia and entrapped muscle tissue associated with oculocardiac reflex, significant globe displacement threatening vision and marked extraocular motility restrictions.[8] In the COVID-19 era, you can consider delaying surgeries for those without proven entrapment, leaving repair of enophthalmos or hypoglobus for a

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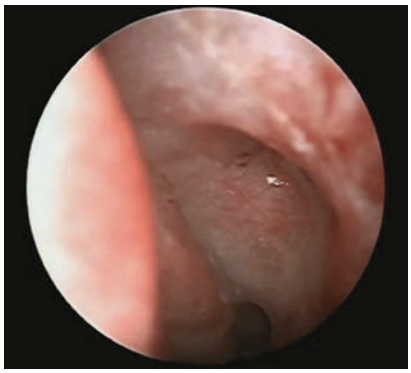
later date, but this should be weighed against the technical challenges presented by delayed orbital scarring. It thus becomes difficult to propose clear guidelines in our field, and all orbital surgery cases must be considered individually in terms of their potential risks and benefits.

Telemedicine

Despite these significant challenges, our patients remain our priority. Fear, anxiety and anger are now well-documented among patients and providers during the COVID-19 pandemic.[9] Patients may no longer be making office visits out of fear for their own safety, while providers may close practices for similar reasons. To reopen and maintain our practices, we need to send a message to our patients that every precaution is being taken in our decision to work, and that we're still available to them. To achieve this, we'll need to incorporate telemedicine wherever possible. This may be the only way to prioritize our public health while ensuring patients unwilling to come into the office are provided the best possible care under the circumstances.

Telemedicine has been shown to work particularly well in ophthalmology in general and oculoplastics in particular. Data from an ocular teleconsultation program has suggested that oculoplastic consultations made up nearly two-thirds of teleconsultations that included photographs.[10] In other contexts, oculoplastics clinics successfully employed telemedicine for initial aesthetic consultations and follow-up appointments for myogenic ptosis, which improved patient flow and revenue.[11,12]

Telemedicine transfer of live images and videoconferencing have also been broadly studied for diagnostic accuracy. In a systematic quality assessment, telemedicine was found to be comparable to in-person visits in various subspecialties of ophthalmology, including oculoplastics.[13] The dermatology literature similarly supports the use of telemedicine for inpatient consult triaging and consultations of skin lesions suspected to be malignant.[14,15] Taken together, there is a broad role for telemedicine across many types of visits in oculoplastics. It would be reasonable to extend the use of telemedicine to triage other conditions such as eyelid lesions and proptosis. We could institute a two-tiered approach to triage via telemedicine and offer in-person visits only for those patients who need it.



Aerosolizing procedures that involve the sinuses and respiratory droplets, such as dacyrocystorhinostomy, put the oculoplastics surgeon at higher risk of coronavirus infection. *(Image: Yan-Hui Cui, Cheng-Yue Zhang, Wen Liu, et al. Endoscopic DCR to treat congenital nasolacrimal canal dysplasia. BMC Ophthalmology (open access) 2019;19:Article number: 244)*

Looking beyond this pandemic, telemedicine may provide long-term benefits for our practices. In addition to improving triage and flow, as well as generating revenue, telemedicine can also improve patient access, particularly in rural areas where there are deficits of subspecialists.[16,17] Physicians may be wary of telemedicine, cautious of the potential liability that could stem from diagnosing conditions without an in-person physical exam.[18] There are data to suggest that telemedicine may not increase rates of malpractice claims due to its low-risk nature, but these studies don't address complex diagnoses such as trauma or orbital tumors.[19] Many payers already cover some types of telemedicine, but important challenges remain, such as reimbursements rates and coverage across state lines. New legislature will need to evolve to address these issues of liability and coverage before telemedicine can truly become mainstream. State laws that limit prescriptions for telemedicine providers would also need to be updated accordingly.

In the short-term, some of these restrictions were addressed by the Coronavirus Aid, Relief, and Economic Security (CARES) Act. These changes allow providers to prescribe controlled drugs by telemedicine in accordance with federal and state government policies, waive requirements of pre-established relationships for Medicare coverage, allow certain health plans to cover telemedicine without a deductible, enhance reimbursements for telemedicine services and fund programs to increase telemedicine access in rural health clinics and non-profit hospitals.[20] These efforts are designed to temporarily mitigate both the liability and cost of telehealth for providers. Oculoplastic providers in rural areas and not-for-profit hospitals should take advantage of these changes to establish telemedicine components in their practices. If applied thoughtfully, these changes may serve as a catalyst to promote adoption of telemedicine more broadly.

Financial Aid Review

The financial implications of COVID-19 are far-reaching, and force us to reexamine many aspects of how we practice, including the financial end of things. Here's a review of some of the recent financial lifelines some practices were able to make use of.

The CARES Acts, through the

Small Business Administration, have allowed private practitioners to apply for loans through the Paycheck Protection Program. This provided oculoplastic practices with fewer than 500 employees, sole proprietors, and individuals loans of up to 250 percent of an average monthly payroll cost for eight weeks, up to $10 million, at a maximum interest of 4 percent. Borrowers were further eligible for loan forgiveness if the funds were used for eligible expenses (payroll costs, mortgage or utility costs) within the first eight weeks, with a reduction if there are layoffs or wage reductions to employees.

For practices with more immediate needs, such as sick leave for employees, rent or mortgage payments, an alternative loan program was the Economic Injury Disaster loan, which provided an up-front advance of $10,000 within three days and loans at a rate of 3.75 percent for small businesses and 2.75 percent for private nonprofits.[21] The U.S. Department of Health and Human Services also administered a Provider Relief Fund program to provide grants to practices or individuals with increased costs or lost revenue from COVID-19.

Finally, there is an employee retention tax credit, equal to 50 percent of qualifying wages that an employer pays their employee in a calendar quarter.[22] Together, these changes helped make it easier for providers to minimize in-office staff while retaining them on the payroll.

Technology Solutions

Our response to this crisis today can dramatically impact our specialty in the long term. We may see multiple waves of this disease, and the changes we implement today may need to remain in place for years. COVID-19 may provide the necessary push for doctors and payers to embrace the options that information technology can offer.[23] In addition to using telemedicine, we imagine a future in which doctors can take advantage of machine learning and artificial intelligence, which have been particularly impressive in ophthalmology for diagnosing a variety of retinal conditions.[24,25] In oculoplastic surgery, machine learning may use photographs to guide procedure selection and operative decision-making.[26] It may help us discern more from histories and images, and rely less on limited virtual physical exams. Finally, the pandemic may force our nation to re-examine payment models, which currently place financial burdens on practices when procedures are postponed.

In conclusion, COVID-19 is unlike anything most of us will ever see in our lifetimes yet, despite its tragedy, it's a unique opportunity for us to evolve. While many of these changes are temporary, they still represent efforts to maximize patient care while maintaining revenue and minimizing legal risk. Seeing these changes as an opportunity to make a long-standing impact in our specialty will ultimately benefit both patients and providers. This is the silver lining in these trying times, and we should seize the opportunities that it provides with an eye toward a better future. REVIEW

Dr. Kim is an ophthalmology resident at the University of Pennsylvania's Scheie Eye Institute. Dr. Briceño is an oculoplastics specialist at Scheie and an assistant professor of clinical ophthalmology at the University of Pennsylvania's Perelman School of Medicine.

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New Mid-Year Codes And Regulations

July is here and that means some mid-year updates from Medicare take effect. Here's what you need to know.

Q Are there any new codes?

A Yes. The Health Care Procedure Coding System (HCPCS) gets releases in both January and July. All of the following codes are in effect as of July 1, 2020; the first three are for the various parts of reporting remotely-performed OCT of the retina (the measurement is done by the patient).

- 0604T—Optical coherence tomography (OCT) of retina, remote, patient-initiated image capture and transmission to a remote surveillance center unilateral or bilateral (this is for the initial device provision, set-up, and patient education on the use of the equipment).
- 0605T—The same as 0604T, but this code is used by a remote surveillance center which provides technical support, data analyses and reports, with a minimum of eight daily recordings, over a 30-day time span.
- 0606T—The same as 0604T, but covers the review, interpretation and report by the prescribing physician or other qualified health professional of remote surveillance center data analyses over a 30-day time span.

Note: Don't report 0604T, 0605T, 0606T in conjunction with 99457 or 99458.

The next code is:

- 0615T—Eye-movement analysis without spatial calibration, with interpretation and report (don't report 0615T in conjunction with 92540, 92541, 92542, 92544, 92545, 92546 or 92547).

The next three codes are for actually implanting an artificial iris in different clinical settings. A device code (C1839) was already established for use in January 2020. The device code itself has pass-through payment status under Medicare and you should report both the device code and one of the codes listed below.

- 0616T—Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed without removal of crystalline lens or intraocular lens, without insertion of intraocular lens. Use this code when you perform only the artificial iris implantation.
- 0617T—This code is for artificial iris implantation and removal of the crystalline lens with insertion of an IOL (don't report 0617T in conjunction with 66982, 66983, 66984).
- 0618T—This code is for artificial iris implantation with secondary intraocular lens placement or intraocular lens exchange (don't report in conjunction with 66985 or 66986).

Note: Don't report 0616T, 0617T, 0618T in conjunction with 66600, 66680 or 66682.

Since the above codes are new and, as of this writing, there's no published coverage or payment information, be sure to check your Medicare Administrative Contractor's website after July 1 for updates.

Q I'm still dealing with significant issues due to

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COVID-19 and I think it might affect my ability to report 2020 MIPS data. I don't want to be penalized in the future. Is there any help available in this area?

A Yes. In mid-June, CMS made two hardship exceptions available for the 2020 performance year. The first applies only to the electronic medical records area of MIPS (known as Promoting Interoperability, or PI). While there are a number of possible reasons to consider this hardship exception, CMS does state that one of the possibilities is that you "face extreme and uncontrollable circumstances such as disaster, practice closure, severe financial distress… ." If granted, you would have this MIPS area, which makes up 25 percent of the total scoring, re-weighted unless you later choose to submit data in this category.

The second hardship exception is broad, and is defined as being for "Extreme and Uncontrollable Circumstances." CMS notes this might be considered in the following scenarios:

- you're unable to collect information necessary to submit for a MIPS performance category;
- you're unable to submit information that would be used to score a MIPS performance category for an extended period of time (for example, if you were unable to collect data for the Quality performance category for three months); and/or
- the circumstances impact your normal processes, affecting your performance on cost measures and other administrative claims measures.

If the second hardship exception is granted, all four MIPS categories are re-weighted to 0 percent and you're not penalized in 2022—but you can't earn a bonus unless you later decide to submit data for 2020 and subsequently achieve a big enough MIPS score.

You can access the information and applications for these hardship exceptions at https://qpp.cms.gov/mips/exception-applications. You can apply for these exceptions through December 31, 2020.

Q Is there any new information on the 2021 ICD-10 codes that come into effect in October 2020?

A While it's not final as of this writing (but will be soon), the panel in charge of the new and revised codes met in March and posted their minutes on the official CDC website. A sampling of the new proposed codes that affect ophthalmology are as follows:

(Continued on page 63)

A middle-aged woman turns to Wills Eye Hospital for help with unexplained ocular swelling.

Ollya V. Fromal, MD, and Jurij R. Bilyk, MD

Presentation

A 39-year-old woman presented to Wills Eye Hospital with a three-month history of swelling near the inner corner of her right eye. She reported severe pain over the right cheek, tearing and sinus congestion. She denied eye discharge, changes in visual acuity, numbness, diplopia, epistaxis, fever, chills or weight loss.

Medical History

The patient had no significant past medical history. She delivered a healthy child six months prior to presentation via cesarean section and was breastfeeding at the time of her initial visit. Her only medications were oral contraceptives. Family history was noncontributory. The patient denied alcohol, tobacco or illicit drug use, and had no known drug allergies.

Examination

Visual acuity was 20/25 on the right and 20/20 on the left. Pupils were equal, round and reactive without afferent pupillary defect. Extraocular motility was full bilaterally. There was no globe dystopia or lagophthalmos. A 2.5 x 3.5 cm, tender, firm, raised mass with overlying skin hyperpigmentation was present inferior to the medial canthus on external examination of the right eye (*Figure 1*). There was no crepitus or fluctuance on palpation of the lesion. No mucous or bloody discharge was noted with lacrimal sac and mass massage. Facial sensation was intact bilaterally. Slit lamp and funduscopic examinations were normal bilaterally.

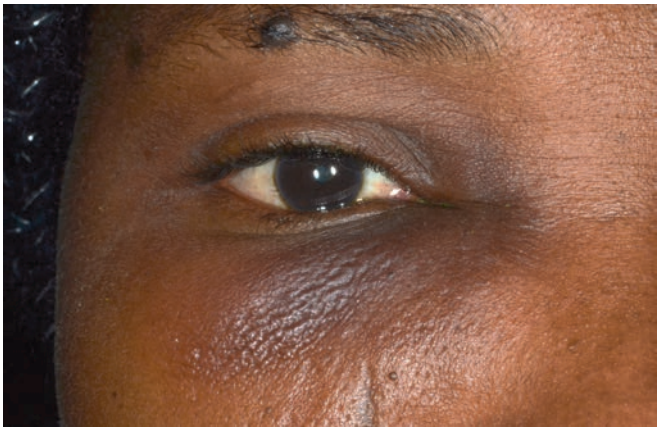

Figure 1. External color photograph of the right eye and ocular adnexa of the patient, demonstrating a pericanthal mass with overlaying skin hyperpigmentation and lichenification.

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

(Continued from page 61)

- we may finally get a "real code" for pseudoexfoliation of the lens not involving glaucoma in the H27.81 area;
- Stargardt's Disease appears destined to get its own code in the H35.55 area; and
- minor changes may be made to the Z01 area and the Z79 area.

Q Are there any July 2020 National Correct Coding Initiative (NCCI) edits that affect ophthalmology?

A There's one in particular that eye surgeons should be aware of. The code combination of 66174 (Transluminal dilation of aqueous outflow canal; without retention of device or stent) and 65820 (Goniotomy) has a new "mutually exclusive" edit, which means that the codes can't be billed on the same eye in the same surgical session. Before July 1, 2020, there were no NCCI edits bundling these two codes, which meant offices and ASCs could still bill both codes together. However, CPT's publisher, the American Medical Association, via its CPT Assistant publication, noted in December 2018 and September 2019 that the codes shouldn't be billed together. As a result of the new NCCI edits, AMA and CMS now agree that even if you do perform both procedures, you should only bill for 66174. It's also likely that other payers will agree, but you should check.

In terms of payment, looking at national Medicare payments, this negatively affects surgeons (a loss of about $400). ASCs would get a $459 reduction. Hospital outpatient department claims won't change at all, due to the way the comprehensive Ambulatory Payment Classification works, which only pays for one of the codes anyway.

Q I've seen some discussion about having patients pay us for the extra cost of all the personal protective equipment we need to have to protect everyone (staff, doctors and patients) from coronavirus infection.

A Unfortunately, supplies used to care for your patients are already part of your claims and payment. No charge to the patient is warranted, either. REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Atlanta. He welcomes any comments or questions on the topic of this month's column. Please contact him at plarson@corcoranccg.com.

Workup, Diagnosis and Treatment

The patient's clinical history and presentation were suspicious for an inflammatory or neoplastic lesion of the lacrimal system. The differential diagnosis included a host of inflammatory etiologies, including sarcoidosis, granulomatosis with polyangiitis, IgG4-related ophthalmic disease and Langerhans cell histiocytosis. Lymphoproliferation (including lymphoma), lacrimal sac carcinoma or inverted papilloma, dermatofibroma and various mesenchymal tumors were also considered. Bacterial infectious etiologies such as dacryocystitis, orbital cellulitis, orbital abscess and ethmoiditis were thought to be less likely, given the chronicity of the symptoms, though atypical infections, including fungal etiologies, were possible. Serologic testing was ordered, with resultant normal values for angiotensin converting enzyme, lactate dehydrogenase, complete blood count with differential, total immunoglobulin (Ig)G, IgG4 subclass and cytoplasmic/perinuclear/atypical perinuclear antineurophil cytoplasmic antibodies.

Computed tomography of the orbits and paranasal sinuses was ordered and revealed mass-like soft tissue thickening in the right medial canthus and malar soft tissue, with erosion of the right orbital floor and nasolacrimal duct, as well as the medial and anterior walls of the right maxillary sinus *(Figure 2)*. Mild infiltration of the inferior extraconal fat and complete opacification of the right maxillary sinus were also noted.

The bone eroding characteristics of this ill-defined mass were highly suspicious for a malignant process originating in the right maxillary sinus or lacrimal sac. The patient underwent a transnasal endoscopic biopsy of the lesion in the operating room. All frozen tissue specimens were consistent with an inflammatory process without evidence of neoplasia. Given the high suspicion of malignancy, a transconjunctival exploration was also performed to maximize diagnostic yield. Permanent pathologic examination of the orbital and sinus tissue revealed marked fibrosis with vaguely storiform areas, obliterative phlebitis and lymphoplasmacytic infiltrate rich in IgG4+ plasma cells *(Figure 3)*. No malignant characteristics were present. Based on the pathologic characteristics, diagnosis of the IgG4–related disease (IgG4-RD) was made.

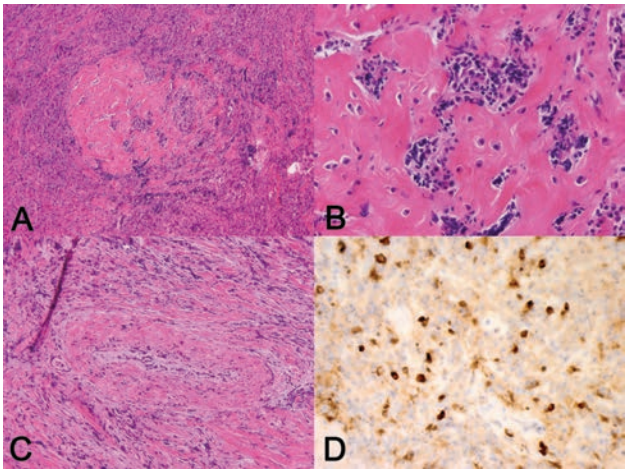

Figure 3. H&E slides showing storiform fibrosis with dense plasmacytic infiltrate (A), plasma cell aggregates (B), and obliterative phlebitis (C). Immunohistological staining (D) demonstrating numerous IgG4+ plasma cells.

The patient was referred to a rheumatologist for a systemic evaluation and initiation of immunosuppressive therapy. Additional laboratory tests were performed and were found to be within the normal range, including myeloperoxidase, proteinase 3, anti-Ro/anti-La antibodies, thyroid stimulating hormone and thyroxine. The Westergren erythrocyte sedimentation rate and C-reactive protein level were elevated at 51 mm/hr and 21 mg/L, respectively. A CT of the chest, abdomen and pelvis revealed no evidence of IgG4-RD elsewhere. Before initiating immunosuppressive therapy, tuberculosis screening was performed with

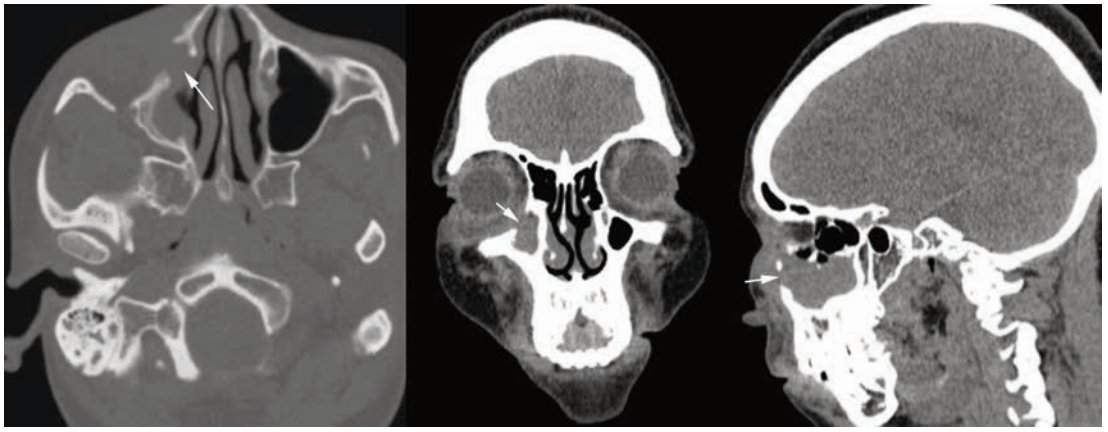

Figure 2. Axial (left), coronal (middle) and parasagittal (right) CT images demonstrating the soft tissue mass, right maxillary sinus opacification, and bone erosion (arrows).

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REVIEW Advertising Index

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Quantiferon gold, with a positive result. The infectious disease consultant recommended rifampin therapy for latent tuberculosis, given the patient's breastfeeding status. Oral prednisone was started two weeks following initiation of rifampin.

At the one month follow-up visit after initiation of corticosteroid therapy, the patient's ocular symptoms and exam showed noticeable improvement. MRI of the orbits showed stable orbital disease. However, because of a progressive elevation in the ESR and CRP, the patient's rheumatologist recommended a steroid taper and began rituximab infusions. Three months later, the patient reported an additional significant relief in periorbital pain. Examination demonstrated continued improvement in pericanthal edema. Mild skin lichenification was noted over her cheek, but the area was no longer tender to palpation. Repeat MRI imaging displayed no progression of her sinoorbitopathy.

Discussion

IgG4-RD is an inflammatory disorder affecting one or several organ systems, characterized by significant fibrosis. It was first described in Japan in 2001 in patients with autoimmune pancreatitis (AIP) and increased serum IgG4 levels.[1] It was later observed that similar lesions were found in extrapancreatic sites in many patients with AIP.[2,3] Histopathologically, IgG4–RD is characterized by tumefactive lesions with obliterative phlebitis, storiform pattern fibrosis and dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells.[3]

Nearly one quarter of IgG4–RD cases in the United States have ophthalmic manifestations.[4] When the disease affects the periocular region, it's referred to as IgG4-related ophthalmic disease (IgG4-ROD). IgG4–ROD affects males and females equally, with mean age of onset of 55.[5] Pediatric cases are rare.[6]

IgG4-ROD comprises 5 to 20 percent of all inflammatory orbital lesions.[7] The lacrimal gland is affected in at least half of all cases, but there can also be involvement of the trigeminal nerve, extraocular muscle, orbital fat, eyelid and lacrimal drainage system.[4,7] Sensory nerve infiltration is common, and bilateral infraorbital nerve involvement is a very specific feature of the disease.[3] Presentation of IgG4-ROD is variable and dependent on the anatomy. Painless proptosis, restrictive strabismus with diplopia and compressive optic neuropathy have been described.[8]

MRI usually demonstrates a T1 isointense and T2 hypointense infiltrate that enhances with contrast administration.[9] Bony destruction is rare, but possible, as demonstrated in our case.[9] Of note, serum IgG4 levels are normal in 30 to 40 percent of patients.[10] Moreover, increased serum IgG4 levels and presence of the IgG4+ plasma cell on immunohistochemical studies aren't specific to IgG4-RD. Histologically, there may be an overlap between IgG4–RD and other inflammatory conditions, most notably GPA and reactive lymphoid hyperplasia.[3] In addition, not all histopathologic features of IgG4-RD are necessarily present in lacrimal gland tissue.

The management of IgG4–RD requires a multidisciplinary approach. Systemic corticosteroids are considered first-line therapy, although high relapse rates are common.[11] In such cases, rituximab is the agent of choice. Radiotherapy and surgical resection have met with limited success.[4,12]

Systemic involvement is present in over half of the IgG4–ROD cases and usually affects the salivary glands, liver, retroperitoneum, pituitary, pancreas, bile ducts and nasal mucosa.[3,4] Thus, a thorough systemic evaluation is necessary and usually includes a combination of the following: measurement of pancreatic and liver enzymes; assessment of renal function; CT imaging of chest, abdomen and pelvis; and a lymph node biopsy, if lymphadenopathy is present. As reported in other chronic autoimmune conditions, IgG4–ROD increases the risk of B-cell lymphoma development, specifically extranodal marginal zone lymphoma; this transformation appears to be especially prevalent in East Asia.[13]

In conclusion, IgG4–ROD comprises a significant percentage of orbital inflammatory disease. It has a variable presentation and, as such, should be considered on a differential diagnosis in patients presenting with inflammatory orbital signs and symptoms. Serologic testing is neither sensitive nor specific. Biopsy is required for a definitive diagnosis. Thorough systemic evaluation is necessary in all IgG4–ROD patients, as more than half will have systemic manifestations. REVIEW

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

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

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

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

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

- Hypersensitivity *[see Contraindications (4)]*

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

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

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

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

Rare 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 *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from 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 *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

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

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

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

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

Manufactured for:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

T2019-110

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

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.

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1. Accessed April 17, 2020. **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2019.

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