Medicare Q & A: Medicare public data: Know what's being said about you ***p. 16***

REVIEW® of OPHTHALMOLOGY

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MINIMIZING MEDS IN GLAUCOMA PATIENTS

Drugs are a mainstay of treatment, but some procedures can decrease compliance issues in certain patients.

ALSO INSIDE:

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†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 end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported 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.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

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

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

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **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 [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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NEWS

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JUNE 2021

Tecnis Synergy IOLs Receive FDA Approval

In early May, Johnson & Johnson Vision announced U.S. Food and Drug Administration approval of its new presbyopia-correcting Tecnis Synergy and Tecnis Synergy Toric II IOLs. (The Synergy IOL has been available outside of the U.S. since 2019; all of the Tecnis Synergy IOLs are expected to be available in the United States and Canada this summer.)

According to the company, the Synergy IOLs are based on the existing Tecnis lens platform. The company says the Tecnis lenses use a proprietary combination of materials and design that results in very good visual clarity, lower light dispersion, a very low level of chromatic aberration and extremely low spherical aberration—as well as very good contrast under all light conditions.

Ike K. Ahmed, MD, FRCSC, a professor of ophthalmology at the University of Utah and assistant professor at the University of Toronto, says he's had about a year of experience with the Synergy lens

in Canada. (Dr. Ahmed is a consultant for Johnson & Johnson Vision.) "We've implanted them in about 100 patients," he says. "I've been doing an evaluation of these lenses, and the experience has been good.

"Most multifocals have a very good range of vision, but these have the best I've seen," he explains. "They combine a multifocal design with extended depth-of-focus design. They have diffractive rings, some of which split the incoming light to different focal points, while others stretch the light between focal points. It's kind of like a mix between the Symfony and the Tecnis multifocal. This combination gives patients a true continuous range of vision, as shown by both the defocus curve and what we see clinically. Patients are able to see well from 30 cm all the way out to 80 cm." (In a study sponsored by the company, nine out of 10 patients receiving these lenses didn't need glasses after the surgery.)

"The Synergy lens also has the closest near point of any multifocal I've had experience with," Dr. Ahmed adds. "It's at least 10 or 15 cm closer than others I've used. This lets patients bring things closer and see them clearly without any visual tradeoff."

Dr. Ahmed says it helps that the Tecnis platform uses materials and design that may limit the loss of contrast sensitivity associated with multifocal technology. "These lenses use [what the company calls]

(Continued on p. 9)

IN BRIEF

J&J Vision Announces FDA Approval of Acuvue Abiliti Overnight Therapeutic Lenses
Johnson & Johnson Vision announced the FDA approved Acuvue Abiliti Overnight Therapeutic Lenses. The company says this is the first and only FDA-approved orthokeratology (ortho-k) contact lens for the management of myopia. Abiliti Overnight ortho-k contact lenses are specifically designed and fitted to match the eye based on its corneal shape, to temporarily reshape the cornea. Abiliti Overnight will be available for astigmatic eyes, as well.

Alcon Partners with BlephEx
Alcon announced an agreement that provides Alcon exclusive rights to sell BlephEx technology (a device and eyelid cleaning procedure for removing bacteria and biofilm) and accompanying products in the United States.

Essilor Receives FDA Breakthrough Device Designation for Stellest Lens
The U.S. FDA granted Breakthrough Device designation to Essilor's Stellest spectacle lens, which was developed to correct myopia and arrest its progression.

New Interactive Storybook to Screen for Color Deficiency
The Children's Eye Foundation of the American Association for Pediatric Ophthalmology and Strabismus has unveiled an interactive children's book, *The Curious Eye*, to help screen for color-vision deficiency. The foundation has posted a free digital version of the book online at thecuriouseye.org.

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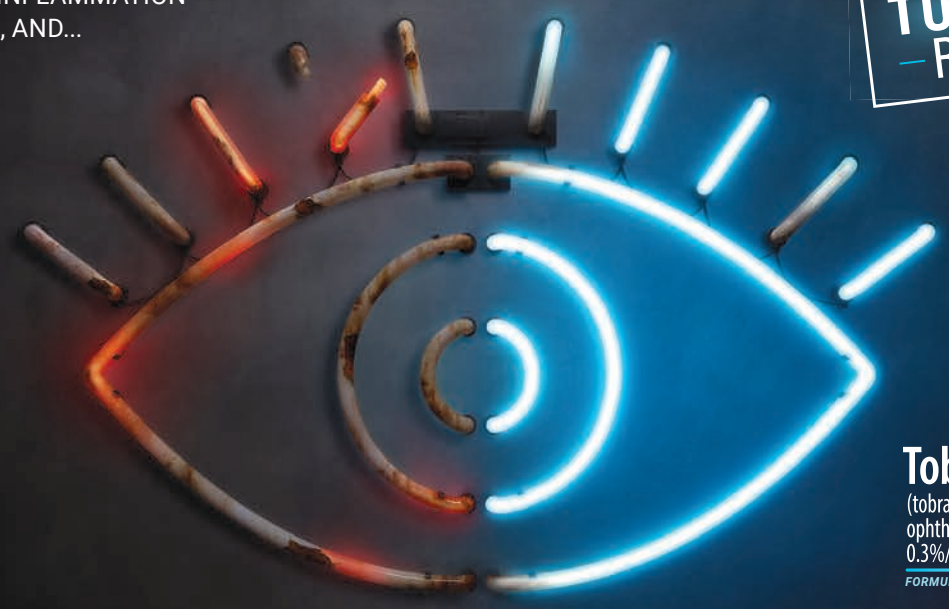

TobraDex® ST
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PRESCRIBE TOBRADEX® ST to control ocular inflammation with risk of bacterial infection

- Rapid relief from blepharitis/blepharoconjunctivitis symptoms[1,a]
- XanGen™ suspension technology provides increased viscosity for improved ocular bioavailability of drug and consistent delivery[2]
- TOBRADEX ST contains half the dexamethasone as TobraDex®, yet similar ocular tissue exposure[2,b]

Eligible patients could pay as little as $45 for TOBRADEX ST
LEARN MORE AT MYTOBRADEXST.COM

Indications and Usage

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

Important Safety Information

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

WARNINGS & PRECAUTIONS:

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

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

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

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

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

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

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

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

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

eyevance pharmaceuticals

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

Brief Summary

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

INDICATIONS AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

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

Hypersensitivity: Hypersensitivity to any component of the medication.

WARNINGS AND PRECAUTIONS

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

Aminoglycoside sensitivity: Sensitivity to topically applied aminoglycosides may occur.

Cataracts: May result in posterior subcapsular cataract formation.

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy and Nursing Mothers

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

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

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

Rx Only

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TST-01-20-MS-05

Tecnis Synergy IOLs Approved by FDA

(Continued from p. 5)

ChromAlign technology to correct chromatic aberration, plus a little violet filtering which may reduce some of the dysphotopsia from LED lights," he explains. "I do ask my patients about their night vision, and they seem to be happy with it."

Dr. Ahmed admits that there are still issues to consider. "This is a diffractive design, so there's a risk of haloes," he says. "I always warn my patients about this, although anecdotally, those receiving the lens seem to be happy with their night vision. Also, compared to a monofocal lens, there will always be some contrast loss. So you have to be mindful of patients who may be at risk for quality-of-vision issues, whether because of comorbidities, work-related issues or lifestyle. Furthermore, it's important to hit the refractive mark. These lenses are very sensitive to refractive errors, so the surgeon needs to hit that plano mark and minimize astigmatism as much as possible.

"Overall, these lenses have been an excellent choice for our patients," he concludes. "We've been very happy with our results using the Synergy lens."

A Breakthrough in Sickle Cell Retinopathy Management

Ophthalmologists at New York Eye and Ear Infirmary of Mount Sinai have developed a new way to evaluate patients with sickle cell retinopathy and assess the disease earlier than previously possible, using optical coherence tomography angiography. In sickle cell disease, abnormally folded hemoglobin distorts the shape of red blood cells, causing them to clump and block blood flow. The resulting capillary damage that may occur in the retina can cause bleeding, retinal detachment and vision loss.

Using sequential OCTA images of blood flow in the retina has allowed the researchers to assess both disease progression and the impact of treatment on the disease. The more the blood flow fluctuates between images, the higher the risk of a permanent blockage. The study authors note that without this technique, it's impossible to judge disease status in the retina until patients report vision loss.

In a small study conducted at Mount Sinai, 13 patients with sickle cell disease—some being treated for the disease, others not—were compared to 14 controls. All subjects were imaged 10 times in a row using OCTA over a 10-minute period; this was repeated an hour later. Sickle cell disease causes vessels to open and close—or "flicker"—so the researchers counted the number of flickers between scans for each patient. They found that patients with no disease had minimal or no flickering, indicating consistent blood flow. Sickle cell patients not receiving treatment had substantially more flickering than patients on treatment, indicating that the treatment was having a beneficial effect. (The study was published in the online May issue of *Biomedical Optics Express*.)

The researchers have used the measurements of flicker frequency and location to develop a computer algorithm that can assess the risk of retinal blood blockages in sickle cell patients. For more information, visit mountsinai.org. ◀

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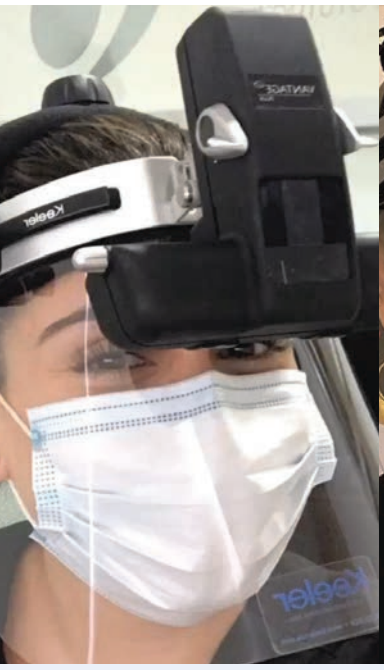


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Dr. Michelle Hammond

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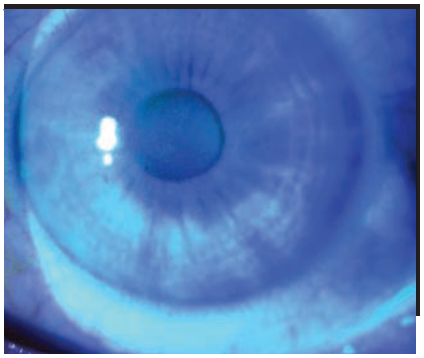
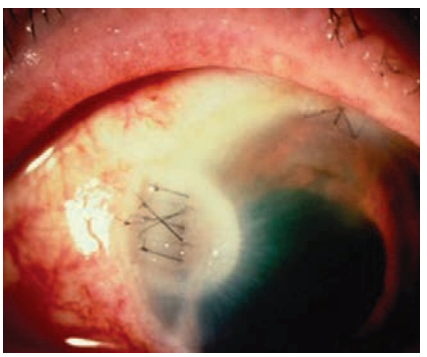
ISSUE FOCUS: GLAUCOMA





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

GLAUKOS®

The Final Curtain

Musings on life, ophthalmology and the practice of medicine.

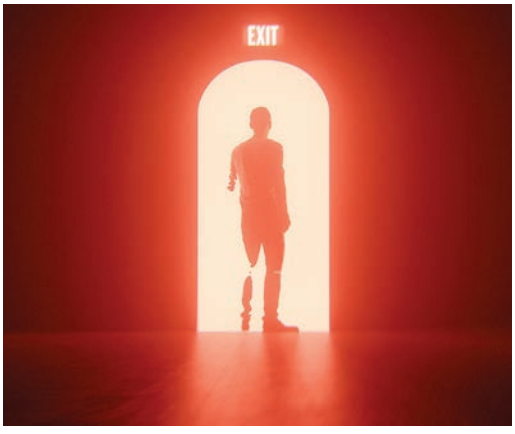
MARK H. BLECHER
CHIEF MEDICAL EDITOR

The myriad issues and stresses of practicing medicine and practicing ophthalmology don't seem to lessen year to year—and most certainly not this past year. For many of our brethren, this was the year to either execute a previously planned retirement or to throw caution to the wind and just chuck it all. And I'm sure there are more than a few younger colleagues who were wishing they could just hang it up.

Aside from our frustration with the lemons life has given us, is the more nuanced question: How do you know when it's time to hang it up? In an otherwise 'normal' year (has there been one recently?), how does one know when it's time to step back from patient care, either surgical, medical or both? When is it time to step back from running the practice? In truth, no one wants to be that doctor who should have stepped down months/years ago. Yet, most all of us have spent our entire careers exceeding expectations, and almost none of us has had someone else tell us what we can and can't do.

And the answer to this question, or at least the implementation of it, depends on your specific practice situation: Private or corporate? Solo or group? Equity or non-equity?

Let me address one of these: Private practitioners, especially solo, who started their practices, are among the most loathe to give them up. No matter that the check from private



equity or the local hospital system has cleared their bank accounts, it's still—in their heads at least—their practice. But then, one day, it isn't and they will have to deal with this new reality—and with the new managers and providers who show up to take over. If we're going to be charitable, we would totally understand. But just like end-of-life decisions in general, the last years in practice are rarely without messiness and drama. I'm surprised that the desire to have a gracious exit doesn't outweigh their ego's need to control things to the end. And trust me, I'm not usually that kind in my assessment of human nature.

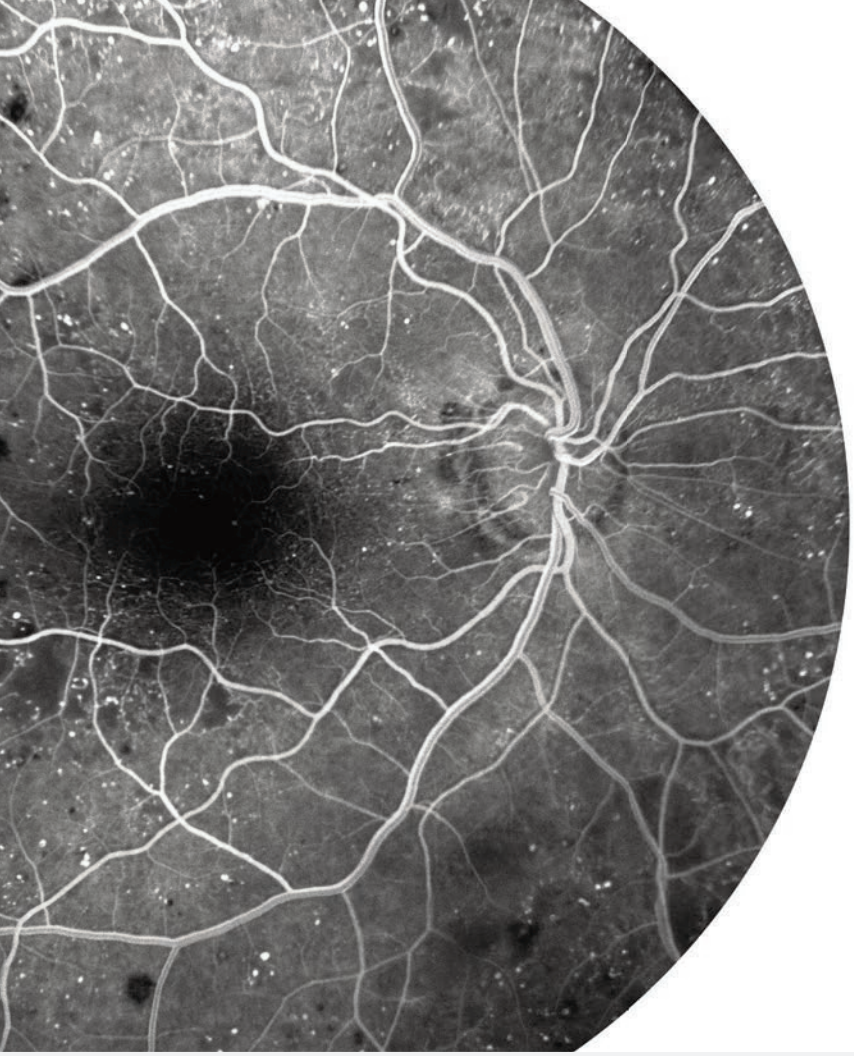
Much has been written about the convoluted relationship between self-worth and work, and the more validation you get from work, the more difficult it is to not become addicted. Let's admit it, ophthalmology is a very rewarding career. How can you not feel gratified, if not superhuman, restoring sight? That's quite an addictive drug. We've all felt that we can't leave our patients unattended, that no one knows or cares for them better. It's tough to get off the merry-go-round.

Add to that those rugged individuals who built their practices from the ground up and then spent 40-plus years creating, nurturing and being lord and master of all they survey. It's extremely difficult to just walk away from that even if it was your choice.

Your practice is like your child, and losing your child isn't something anyone is prepared for. Wrapping your head around the fact that someone else, clearly not as gifted, is going to take your baby's hand and guide it forward can be mind-blowing. Walking away from what you created isn't something you think much about until it stares you in the face. There aren't books or self-help courses specifically for this. Add to that your patients—your friends who came to see you at the same time every year—will now be under the care of strangers … Kids! ... Millennials! … Lord help us. However, this process of stepping down happens to everyone eventually.

So, as the new reality arrives, while you attempt to hold your head high, the benighted ruler abdicating the crown, it's likely all you'll be able to think of saying is:
"Get off my lawn!" ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.



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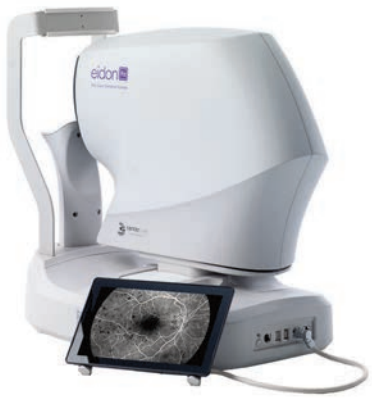

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MEDICARE Q&A

Medicare Public Data: Know What's Out There

Learn what information Medicare's publishing about you and your practice, and how to correct it when it's wrong.

Many of you are aware that some monies (or other recompense) that a physician, teaching hospital, or certain categories of non-physician practitioner receives from pharmaceutical or device manufacturers is made available to the general U.S. public by Medicare through the "Open Payments" program. The purpose of this month's column is to help ensure that you're aware of all the other information the CMS makes public about you and your practice.

Q What information gets reported to Open Payments?

A Some examples of the data that's reported are fees and/or other considerations of value that you received, such as travel/lodging, charitable contributions, royalties, consulting or speaker fees, entertainment and even some research activities. Medicare, in a February 2021 presentation (cms.gov/files/document/open-payments-overview-and-enhancements.pdf), defines these payments/considerations as direct or indirect payments or other transfers of value made to covered recipients (physicians and teaching hospitals), and physician owners or investors, as well as certain ownership or investment interests held by physician owners or investors, or their immediate family members.

The presentation also clarifies that:

- A direct payment is a payment or other transfer of value made directly by reporting entities to a covered recipient (or a physician owner or investor)
- An indirect payment is a payment or other transfer of value made by a reporting entity to a covered recipient (or a physician owner or investor) through a third party, where the entity requires, instructs, directs, or otherwise causes the third party to provide the payment or transfer of value, in whole or in part, to a covered recipient (or a physician owner or investor).

CMS has a good webpage with resources: cms.gov/OpenPayments/Resources. Providers and teaching institutions go to the "Covered Recipients" area.

Q What's the purpose of all this information being available?

A It's mostly about transparency. Some information is still not released, but the trend is to give the public more information so that patients can potentially make informed decisions based on real information and not just take a guess.

Q You noted "Open Payments" has been there awhile. When is the next release of this information?

A Open Payments (cms.gov/openpayments) has been part of CMS' public data release for almost a decade. Usually the release to the public happens every year around June, so by the time you read this it may be out there already. As always, you have an opportunity to see your data and potentially contest it before release; this year the deadline for doing so was May 15, 2021. Even if you didn't check the information in advance, you should definitely go and look at what the general public can see about you. In 2021, CMS will collect information for eventual release on new types of providers such as physician assistants, nurse practitioners and a few others. These new providers don't have their information released and published until 2022.

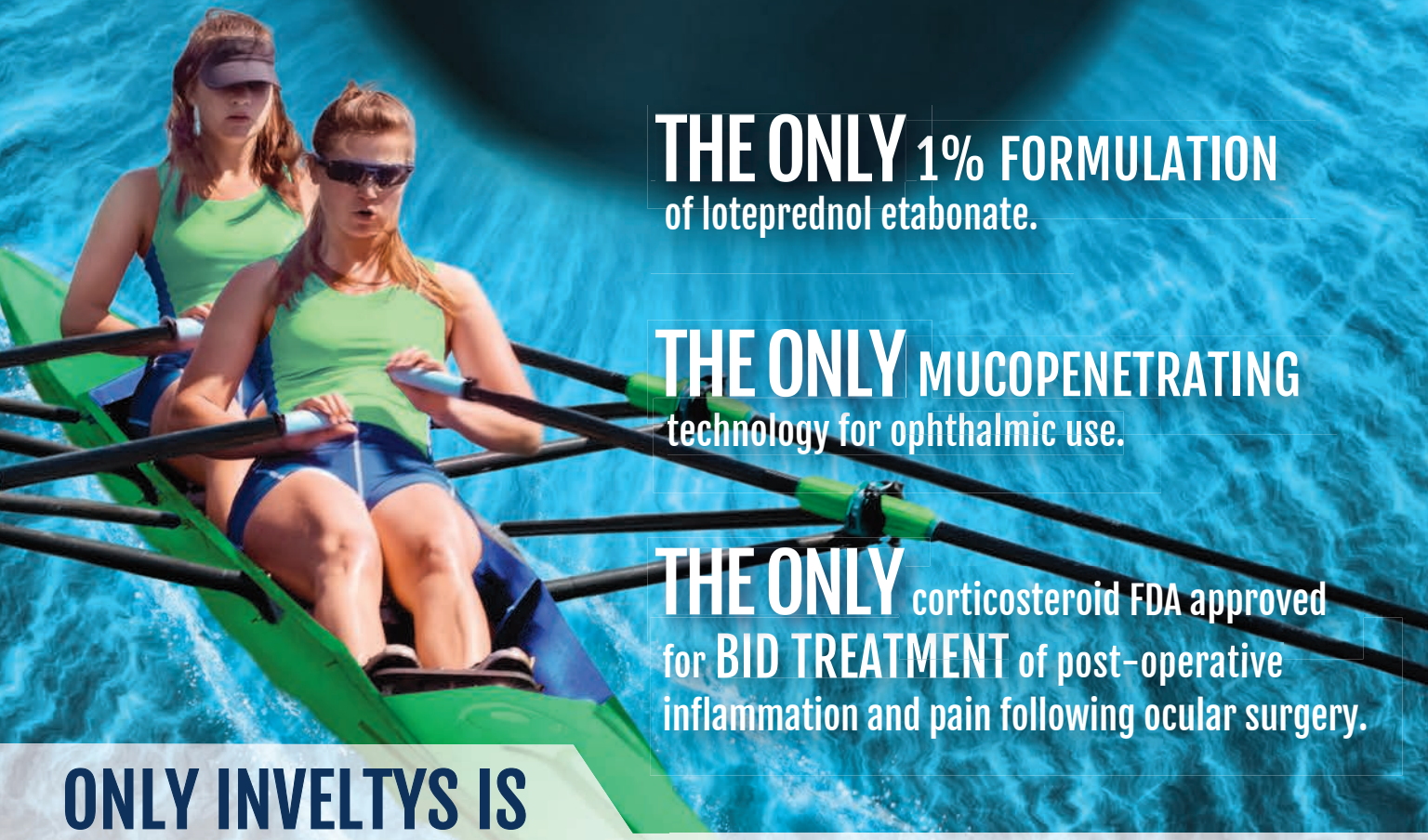
Q Even though the deadline has passed for Open Payments review, how do I dispute incorrect information so it can be corrected for next year's update?

A It's important to know that CMS clearly states that they don't mediate or get involved with disputes; they just relay and then publish what gets sent to them by manufacturers of covered products and some Group Purchasing Organizations. If you disagree with something, CMS notes that you need to work directly with the reporting entities (manufacturers, etc.). There are a couple of things to be aware of, though:

1) You can't just 'go see' without registering in the Open Payments system, which you do by visiting the "Register as a Covered Recipient" website (cms.gov/OpenPayments/

This article has no commercial sponsorship.

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.



THE ONLY 1% FORMULATION
of loteprednol etabonate.

THE ONLY MUCOPENETRATING
technology for ophthalmic use.

THE ONLY corticosteroid FDA approved for BID TREATMENT of post-operative inflammation and pain following ocular surgery.

ONLY INVELTYS IS BID STRONG

Indication

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

INVELTYS 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. If this product is used for 10 days or longer, IOP should be monitored.

Use of corticosteroids may result in posterior subcapsular cataract formation.

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

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

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

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

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

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

INVELTYS®
(loteprednol etabonate ophthalmic suspension) 1%

THERE IS NO GENERIC EQUIVALENT

kala PHARMACEUTICALS

US-INV-2000054

INVELTYS® (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
INVELTYS is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

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

WARNINGS AND PRECAUTIONS
Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. 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—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

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

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

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

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

ADVERSE REACTIONS
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.

Clinical Trial Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse drug reactions in the clinical trials with INVELTYS were eye pain and posterior capsular opacification, both reported in 1% of patients. These reactions may have been the consequence of the surgical procedure.

USE IN SPECIFIC POPULATIONS
Pregnancy—Risk Summary: INVELTYS is not absorbed systemically following topical ophthalmic administration and maternal use is not expected to result in fetal exposure to the drug.

Lactation—Risk Summary: INVELTYS is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to INVELTYS.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility—
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.

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

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

US-INV-2000053 August 2020

Program-Participants/Covered-Recipients/Registration). Once you're in, you can view your present and past data and see instructions for making corrections.

2) Your account stays completely active for 60 days; if you exceed this, you can unlock your account yourself in the CMS Portal.

3) If there's no activity on your account in 180 days, it's deactivated and requires you reach out to the Open Payments Help Desk by email or phone (OpenPayments@cms.hhs.gov; 855-326-8366; for a TTY line, call 1-844-649-2766).

Q Is any of this information about the actual codes that I personally (or as part of my group) got paid for?

A Yes, one of these public releases is officially known as "Medicare Provider Utilization and Payment Data" (cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Physician-and-Other-Supplier). It's often colloquially referred to as the "Medicare data dump," and has been in use since 2012. CMS notes this set of information "provides information on services and procedures provided to Medicare beneficiaries by physicians and other healthcare professionals. The Physician and Other Supplier PUF [Public Use File] contains information on utilization, payment (allowed amount and Medicare payment), and submitted charges organized by National Provider Identifier (NPI), Healthcare Common Procedure Coding System (HCPCS) code, and place of service. This PUF is based on information from CMS administrative claims data for Medicare beneficiaries enrolled in the fee-for-service program …"

The data for each year's release can be sorted and is available in two forms in addition to a couple of summary tables that have aggregated information by physician, state and HCPCS code. The two forms of data are:

1. An online interactive dataset (you can sort and filter data directly without downloading).
2. Tab-delimited file format (requires importing the downloaded information into a database or statistical software; Statistical Analysis System read-in language is included in the download ZIP package).

CMS also notes that this data has some limitations: The "data may not be representative of a physician's entire practice as it only includes information on Medicare fee-for-service beneficiaries. In addition, the data are not intended to indicate the quality of care provided and are not risk-adjusted to account for differences in underlying severity of disease of patient populations …"

Q I heard that there's also a data set that I can use to compare my practice to others. What's that?

A This information has been available since 2010, and is known as the Physician/Supplier Procedure Summary (cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Physician-Supplier-Procedure-Summary). This is basically utilization information about specific codes paid during a recent year by Medicare (not Medicare Advantage or private payers). Importantly, this data can't be sorted for a specific provider; instead it's more general. It can be sorted by specialty, however, so you could use this information to get general benchmarks about the average eye-care practice (optometry and ophthalmology) for codes billed. Non-billed services are not available, of course, as no claims were ever submitted for them. CMS notes the file "… is organized by carrier, pricing locality, Healthcare Common Procedure Coding System (HCPCS) code, HCPCS modifier, provider specialty, type of service, and place of service …"

Importantly, the 2019 data is different due to some new filters applied by CMS which restricted the size of the data available, so it may be less useful than prior years. It's usually available in late summer or early fall.

Q What do I need to know about the Quality Payment Program (QPP) data being released this year for the first time?

A A small amount of this information has been available for the past two years, but in 2021 some additional information about the 2019 QPP results of a practice/provider will be released over the summer. There are two parts to the information, and they're released in different searchable databases: 1) Medicare Care Compare, and 2) Provider Data Catalog.

CMS notes that Medicare Care Compare is designed to "help patients and their caregivers select doctors and clinicians." It includes such things as practice information (physical location, specialty, education/residency and board certification), whether the practice participates in an Alternative Payment Model (APM), some MIPS Star ratings and attestations, as well as any Accountable Care Organization performance.

According to a CMS poster presentation (cms.gov/files/document/2021-cms-quality-conference-poster.pdf) in early March 2021, the Provider Data Catalog is for more research-focused audiences. The Catalog is in tabular format, and will have practice information as well as "Performance information … [on] … MIPS Final Scores and Performance Category scores; clinician utilization data; and aggregate data." Importantly, the scores from the Cost measures don't meet national reporting standards, according to CMS, and won't be released this year. However, your total Composite score will be released, even though the specific data surrounding the Cost measures isn't. ◀

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

36 FAMILY RECIPES

Inspired by a real patient with MEfRVO.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

CLINICALLY SIGNIFICANT VISION GAINS IN MEfRVO ACROSS 3 ROBUST CLINICAL TRIALS

Proportion of patients who gained ≥15 ETDRS letters (primary endpoint) and mean change in BCVA (ETDRS letters) (secondary endpoint) at Month 6 from baseline vs control[1-4,*]

VIBRANT (MEfBRVO)		COPERNICUS (MEfCRVO)		GALILEO (MEfCRVO)	
Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters
EYLEA (n=91)	**EYLEA (n=91)**	**EYLEA (n=114)**	**EYLEA (n=114)**	**EYLEA (n=103)**	**EYLEA (n=103)**
53% vs 27% in the control group (n=90)	**+17.0** vs +6.9 in the control group (n=90)	**56%** vs 12% in the sham control group (n=73)	**+17.3** vs -4.0 in the sham control group (n=73)	**60%** vs 22% in the sham control group (n=68)	**+18.0** vs +3.3 in the sham control group (n=68)

P<0.01 vs control and sham control.

VIBRANT study design: Randomized, multicenter, double-masked, controlled study in which patients with MEfBRVO (N=181; age range: 42-94 years, with a mean of 65 years) were randomized to receive: 1) EYLEA 2 mg Q4 or 2) laser photocoagulation administered at baseline and subsequently as needed (control group). The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

COPERNICUS and GALILEO study designs: Randomized, multicenter, double-masked, sham-controlled studies in patients with MEfCRVO (N=358; age range: 22-89 years, with a mean of 64 years). Patients were assigned in a 3:2 ratio to either: 1) EYLEA 2 mg Q4 for the first 6 months or 2) sham injections (control) Q4 for a total of 6 injections. In both studies, the primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

*Last observation carried forward; full analysis set.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH MEfRVO AT HCP.EYLEA.US

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **3.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **4.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504

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

03/2021
EYL.21.02.0050

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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Reevaluating Your Digital Marketing Strategy

Learn how to take full advantage of digital resources with expert advice.

CHRISTINE LEONARD
ASSOCIATE EDITOR

While marketing itself hasn't changed much over the years, the way it's executed has. Patients today expect a good online experience, so it's important to keep your web presence updated—operationally and content-wise. In this article, you'll learn tips for optimizing your digital marketing efforts to attract and retain both patients and referral sources.

Digital Marketing

"Digital marketing has become a huge tool for growing practices," says Dagny Zhu, MD, medical director and practice owner of Hyperspeed LASIK-NVision in Rowland Heights, California. "Direct-to-consumer marketing is crucial for refractive practices, because many of our services are elective and we don't have a large insurance network of patients to draw from."

She uses what she calls a "push-and-pull" strategy to increase awareness of her brand and draw in patients. "Push marketing is useful for getting your brand out there or prompting people to start thinking about getting LASIK or elective refractive surgery," she says. "In general, it's more expensive because it targets a broader population who may not be looking for eye surgery services. Pull strategies such as Google ads are less expensive because they're targeted and based on the number of views or clicks."

"Any marketing strategy has three basic steps: differentiate; get found; and convert," says Jim Flynn, an AAOE Consultant and executive vice president and chief brand strategist of OneFire, a marketing firm in Peoria, Illinois. "There are many ways to do this, but all three steps are essential."

Differentiate

As you craft or reevaluate your digital marketing plan, in addition to marketing your services, you'll also need to set yourself apart from your competitors. "Differentiating your practice is key," Mr. Flynn says. "Your practice isn't the same as the practice across town. You have something that's unique—maybe it's the way you interact with patients or the way you run your practice. Ensure that your staff understands what this means so they can consistently communicate it to patients. Every other marketing-related thing you do will be more effective."

Get Found (Online)

Online platforms are powerful for attracting younger patients, which is ideal for a practice with a refractive surgery focus. "It's not uncommon for someone to come into the clinic purely because of what they read on Yelp," says Amir Marvasti, MD, of Coastal Vision Medical Group in Orange County, California. "This seems to have become more common than word-of-mouth advertising."

Your choice of platform will be influenced by your target audience. "A common pitfall of digital marketing is having no clear idea of the target audience," Mr. Flynn says. "If you're a general ophthalmologist, your target audience includes all ages, but skewed 65 and older. A LASIK practice, on the other hand, will be marketing to an 18- to 35-year-old crowd, skewing older if they also correct presbyopia.

"Most clients today are using digital media as the largest percentage of their overall media spend," Mr. Flynn says. "There are many platforms for digital marketing, but you shouldn't feel pressured to use all of them—one or two, done well, is sufficient."

Bear in mind that digital platforms usually involve communication of some kind, such as comments, reviews, live chat or direct messaging. "In the post-COVID world, patients have come to expect good digital communication experiences—when they want and how they want," Mr. Flynn notes. "A practice can be

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Dr. Colvard is a surgeon at the Colvard-Kandavel Eye Center in Los Angeles and a clinical professor of ophthalmology at the Keck School of Medicine of the University of Southern California. **Dr. Charles** is the founder of the Charles Retina Institute in Germantown, Tennessee.

competitive just on the basis of being easier to communicate with."

Here's a breakdown of the main components of a comprehensive digital marketing strategy:

• ***SEO.*** Because getting found online nearly always begins with a search engine query, experts say you can't ignore search engine optimization in your digital marketing strategy. Optimizing your website and any affiliated online platforms will increase your chances of appearing on the first page of search results and increase your website's ranking with Google.

"Only 10 percent of people go to the second page of Google results," Mr. Flynn says. "Ninety percent of searches end on the first page, and 70 percent of those people click on one of the top four search results, which are usually paid ads."

Optimizing begins with strong keywords and relevant content. "Patients are asking questions when they search online, so your content needs to answer these questions," he continues. "Using appropriate keywords will increase patients' chances of finding your content. Watch what terms come up when you start typing in the search bar—those are the words people are searching for. You can also search for 'free keyword tools' to find out what keywords people are using."

Dr. Marvasti says his marketing team analyzes keywords and phrases to fine-tune marketing spending. "We'll spend more dollars on the more commonly searched words and phrases," he says. "With geotargeting, we can also see which search terms are used in different neighborhoods." He advises researching your local community and asking for consistent feedback from your patients about what online platforms they use.

• ***Paid search.*** Paid search, such as Google Ad Words, will bring your digital ads directly to people when they're searching. "Again, 70 percent of people click on the first four results, so you want to be up there," Mr. Flynn says.

Google's local search, which often features an interactive map, is another section you'll want to show up in, since your patients are likely to be from the local community. "When we opened new practice locations, we used Google Ads to help to get the word out and attract patients, since our name was new in those areas," says Dr. Marvasti. Mr. Flynn recommends hiring an optimization service for your online platforms, especially if your practice has multiple doctors or locations, which sometimes confuses Google.

• ***Social media.*** Many medical professionals have begun using social media platforms as marketing and educational tools. Advertising with these platforms will cost money, but posting organic content is free.

"Social media is an excellent option not only for advertising your services but for educating and establishing your trustworthiness and expertise as an eye specialist," Dr. Zhu says. "However, it can be more time-intensive to create unique and educational content, compared to traditional marketing. To succeed with social media marketing, it should be authentic to you." Dr. Zhu has created educational videos addressing topics such as LASIK myths, safe contact lens use, home remedies for dry eye and vision development in babies.

Instagram and Facebook are the most used social media platforms for marketing, in part because they have high engagement. This year, the Pew Research Center reported that in the United States 70 to 73 percent of adults aged 18 to 64 and half of adults over 65 said they use Facebook. Self-reported Instagram use was highest among those aged 18 to 29 and 30 to 49 (71 percent and 48 percent, respectively).[1]

Instagram is owned by Facebook. To advertise on either, all you need is a Facebook Business page and the Ad Manager tool. The cost of advertising—cost-per-click—varies, based on factors such as time of year (it tends to increase as the year goes on) or target sex or age group (slightly higher among 18- to 24-year-olds and higher among females than males).[2]

Dr. Marvasti says he advertises on both Facebook and Instagram. "I share patient stories and patient comments, updates on new technology or procedures in the field and information about the technology that I use,"

MARKETING TO REFERRAL SOURCES

Marketing to doctors—whether they're optometrists, general ophthalmologists or subspecialists—requires some adjustments in both strategy and content, but a strong digital presence will still serve you well.

"You need to have what I refer to as 'helping' or 'thought leadership' content on your website in two ways: patient-facing content and doctor-facing content," says Mr. Flynn.

"Patient-facing content that provides accurate, useful information will help patients feel better about their referrals, because it demonstrates that you have a high-quality practice," he says. "It will also help the patient ask intelligent questions about their options and related care or treatment.

"For doctor-facing content, you might include some interesting pathology in a section for doctors on your website, or speak in a video about a diagnosis and discuss the available options. Helping to educate referral sources is important and builds trust," he says.

Dr. Zhu says another way to incorporate doctor-facing marketing is by hosting regular educational webinars and virtual CEs. "These are great ways to get your name out there and foster good relationships," she says.

These may also be in-person events, such as a Saturday or evening CE class taught by the doctor. "It can be as easy as a wine and cheese reception after practice hours," says Mr. Flynn. "Invite doctors from the community, maybe deliver a short set of comments. It's more social than clinical, but a combination of these two has been very successful for practices."

—CL

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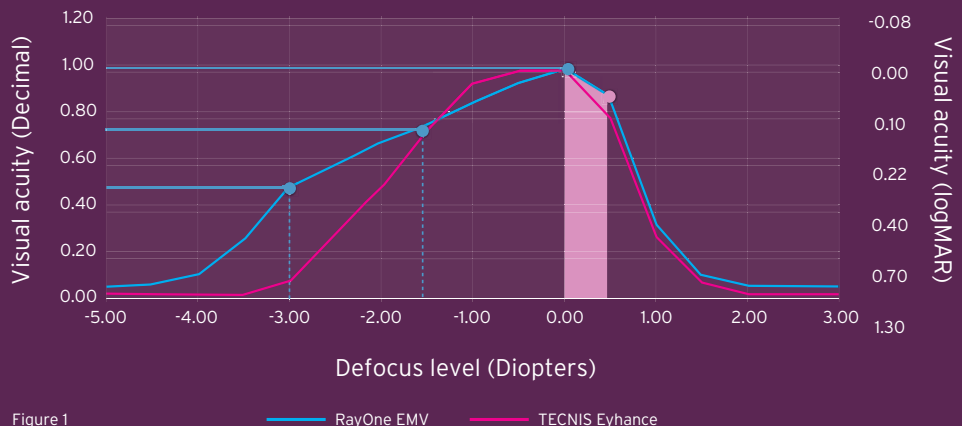

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1. Royo, M. RayOne EMV and TECNIS Eyhance: A Comparative Clinical Defocus Curve. Data on file. 2021.

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he says. "A combination of these has yielded good results."

Mr. Flynn describes paid social media ads as akin to subliminal messages. "It's a branding play," he explains. "The person sees your content just because they ran across it in their feed. They weren't searching for LASIK information, say, but they happened to see it. Then if they do search for it and see your content again, it'll jog their memory and you'll have familiarity on your side. It has conversion opportunities, but it's generally not as high as paid search."

• ***Websites.*** If your website's content management system isn't current, you won't be able to take full advantage of SEO. "Older content management systems don't accommodate some of the off-site technical SEO that's necessary," says Mr. Flynn. "If your website platform is five or 10 years old, chances are it's not optimized for today's browsers—particularly mobile browsers. If you're not optimizing for mobile, you're absolutely disappointing your patients, because they're not getting a good experience with your website. Websites that look and perform like they're out of date won't serve you well."

There are many website platforms, but Mr. Flynn says that WordPress is a popular choice. "Its open-source CMS is optimized for all platforms and it has the largest base of independent contractors and companies that support its CMS," he says. He advises using Google Analytics or Google Tag Manager to track your site's performance.

• ***Quality content.*** In addition to keeping your website's CMS updated with the latest software upgrades, you'll also need to post regularly to ensure your site ranks well with Google. "There are three types of content: evergreen content; fresh, relevant content; and downloadable content," Mr. Flynn says.

"Evergreen content is content on your webpages that's accurate the day it's written as well as six months in the future, or even a year from now," he says. "The second type, known as 'fresh, relevant content' is rated very highly by Google's latest algorithm. Relevance by Google's standards is when people find the site through appropriate keywords and stay on the site. Google likes it when people stay on a site because that means there's good-quality content. Fresh, relevant content increases your quality score with Google, and Google then raises your page's organic rank. If people bounce off your site quickly, that lowers your organic ranking."

He says the best way to deliver fresh, relevant content is on a blog. "Post short articles —500 to 750 words—once or twice a week," he advises. "Google likes changing content—the 'fresh' part—posted on a regular basis."

"We write blog posts in response to frequently searched questions and phrases," Dr. Marvasti notes. "For example, 'can I get LASIK if I'm planning to become pregnant?' or 'LASIK and dry eye' are common topics people search for, so we make a blog post, put it on our website and link it to Google Ads."

Downloadable content is another strong conversion tool. "Using your thought leadership as a medical provider can convert site visitors into leads into patients," Mr. Flynn explains. "An example of downloadable content is an ebook. If you're a LASIK surgeon, this ebook might be on the 10 most important things for understanding if LASIK is right for you. A person will come to your website because they see that ebook, or they see it offered in a blog post that discusses LASIK. The landing page for the ebook may have a form to fill out, asking for first and last name and email address. When patients submit the form, they can download the ebook, and now the practice has a lead it can nurture with more content." In this case, Mr. Flynn says don't forget to include a privacy statement, seeking permission for the practice to communicate electronically with the person.

Building A Marketing Team

Your marketing team makeup will depend on your practice's complexity (i.e., the size of your practice, and the number of doctors and subspecialties). If you have a practice administrator, they may oversee marketing on a strategic and accountability level, but they generally won't have time to be running the strategic portion of marketing. "You'll likely need an internal marketing person," Mr. Flynn says. "Who you hire will determine which outside resources you engage with (e.g., web developer, ad agency, media firm). A mix of internal and external expertise works best.

"A successful marketing program requires a lot of different skillsets," he continues. "It's difficult to get somebody who ticks all the boxes. Generally, I see practices wanting to hire an introductory-salary-level person because they believe young people understand social media. A new college graduate may very well understand social media, but that doesn't mean they understand marketing or monetizing social media. Understanding how to use the tool is different than being able to use it to market effectively.

"You need to have somebody who's part strategy, part technical website builder, part Google Ads manager and part analytics," he continues. "It's difficult to find that all in one person, and very few entry-level-salary individuals have those skillsets. Another challenge is what to do about turnover. How do you back yourself up if your main marketing person leaves? It's important to have a plan so your marketing doesn't go dark for several months." ◀

1. pewresearch.org/internet/chart/who-uses-facebook-instagram-linkedin-and-twitter. Accessed April 28, 2021.
2. adespresso.com/blog/instagram-ads-cost. Accessed April 28, 2021.

DISCLOSURES

Drs. Zhu and **Marvasi** have no related financial disclosures. **Mr. Flynn** is the executive VP and chief brand strategist of the marketing firm OneFire.

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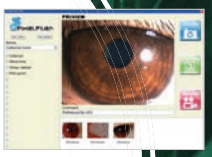

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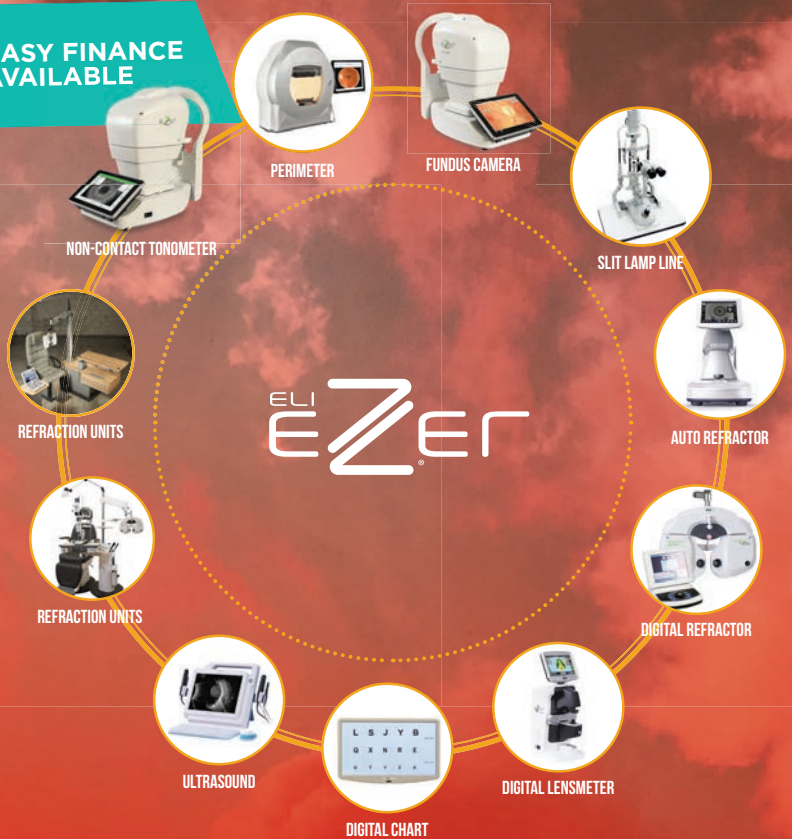

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GETTING STARTED WITH PRIMARY SLT

Primary selective laser trabeculoplasty is growing in popularity around the world. If you're thinking about offering this treatment, here's guidance.

CHRISTINE LEONARD
ASSOCIATE EDITOR

Primary selective laser trabeculoplasty for lowering IOP has become more widespread in the past few years. The laser targets the pigmented chromophores in the trabecular meshwork to produce results comparable to those of argon laser trabeculoplasty but with far less coagulative damage. Additionally, SLT can be repeated, further reducing the problem of compliance among patients who would otherwise rely on daily drops. In this article, clinicians and those at the forefront of SLT research share their experiences and offer guidance for achieving the best results with the laser.

When to Use SLT

SLT can be used as a primary therapy or as an adjunct treatment at any point in the glaucoma treatment paradigm, even after incisional surgery such as a tube shunt or trabeculectomy, as long as you have access to the TM. However, using it as a first-line therapy will produce the greatest effects.

"If you catch a patient early enough in mild to moderate disease stages, you may be able to delay the need for drops and also reduce the need for surgery quite significantly, within a given time frame," says Gus Gazzard, MD, FRCOphth, director of the Glaucoma Service at Moorfields Eye Hospital and a professor of ophthalmology and glaucoma studies at University College London.

Experts estimate that SLT used as a first-line treatment can reduce IOP on the order of 25 to 30 percent, on average, with higher baseline pressures resulting in greater levels of IOP reduction. "A typical POAG or ocular hypertension glaucoma patient with an IOP in the low to mid 20s can expect around a five- to six-point drop," says Thomas E. Bournias, MD, director of the Northwestern Ophthalmic Institute and an assistant professor of clinical ophthalmology at Northwestern University School of Medicine. "This typically occurs in 80 to 90 percent of patients. If a patient has pseudoexfoliation or pigment dispersion, you can expect a higher rate of success and greater pressure reduction. It should be done more as a first-line treatment, and we should be pushing for this more than we are."

Patient Selection

SLT has traditionally been used when drops fail or compliance is an obstacle, but this paradigm is changing, based on new published data. "Since the publication of the Laser in Glaucoma and ocular Hypertension Trial (LiGHT) in 2019, there's been an increasing expectation that SLT can be used first-line,"[1] says Dr. Gazzard, who is also the trial's chief investigator. "The European Glaucoma Society and the AAO's new Preferred Practice Guidelines published this year elevated SLT from a second-line treatment to a primary first-line treatment. A recent paper also showed that well over half of glaucoma specialists routinely use SLT first-line for OAG and ocular hypertension."

"My general approach to patients newly diagnosed with glaucoma is to look for reasons not to do SLT rather than reasons to do it," explains Tony Realini, MD, MPH, a professor of ophthalmology and a glaucoma specialist at West Virginia University. "It's my default, primary therapeu-

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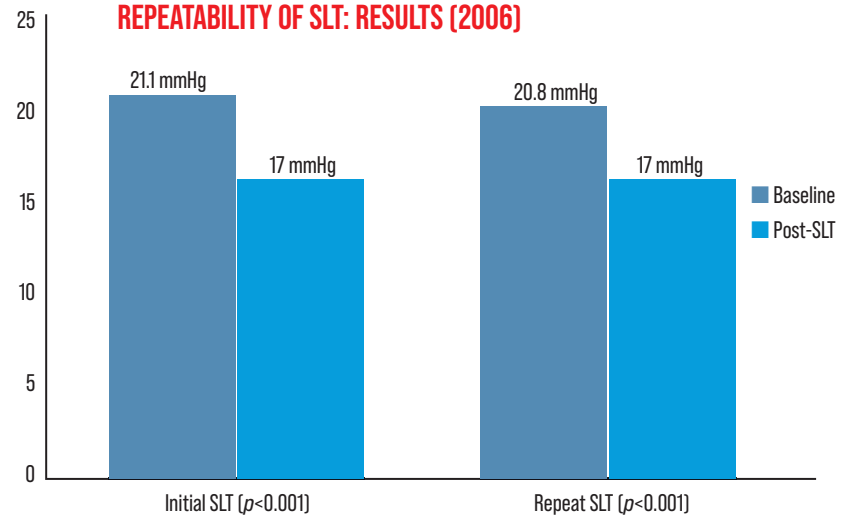


Thomas E. Bournias, MD, et al.

tic option because the clinical data suggest it works at least as well as medication and that it's at least as safe as, if not safer and more cost-effective than, medications. While we don't have adequate instruments to measure certain glaucoma therapies' effects on quality of life, it's unquestionable that patients have better quality of life when off drops than on them."

SLT is suitable for patients with mild to moderate POAG, ocular hypertension, pigment dispersion syndrome and pseudoexfoliation; even if they have some PAS. "SLT may be viable in eyes with NTG, but I don't use it in eyes with untreated pressures less than 15 mmHg," says Dr. Realini. "I've used it in eyes with steroid glaucoma with mixed success. SLT isn't feasible, practical or indicated in eyes with angle closure glaucoma, and it's of questionable use in eyes with inflammatory glaucoma—you don't really want to stir up any more inflammation, although others argue there's little harm in adding a bit more. I've used it in eyes when the next or alternate step was surgery, in the hopes of avoiding surgery. It's a reasonable Hail Mary if the next treatment step is worse, but SLT isn't my first-line in those eyes. Deal with these on a case-by-case basis, when the risk/benefit analysis favors SLT."

"I've done SLT effectively on a uveitic glaucoma patient once, when we were out of options and they refused surgery, but generally they aren't ideal candidates," Dr. Bournias notes. "Also, avoid using SLT on patients with neovascular glaucoma or high venous pressures and those with ICE syndrome, as they have a membrane growing over the TM."

"For very severe cases of glaucoma, it's likely that laser on its own won't be enough," Dr. Gazzard cautions. "The combination of laser and drops for severe cases, and just laser for mild to moderate, is the main paradigm, and it's very powerful."

Patient Counseling

"I offer my patients the option of drops or laser, hoping they'll choose laser first, for compliance reasons," says Dr. Bournias. "If they're unsure, we try drops. I point out that if SLT doesn't work, it won't cause any problems. That helps many patients feel more comfortable making the choice.

"I also tell them about the published studies," he continues. "The Glaucoma Laser Trial in the 80s showed that patients who had laser first versus timolol averaged about a 1.2-mmHg lower pressure after seven years.[2] In the LiGHT trial in Britain, 75 percent of patients who had SLT first were controlled after three years with no medication (many of these patients required only one laser treatment), 93 percent reached the target IOP and none needed glaucoma surgery over the three years, as opposed to about 11 who started with meds."[1]

Patients under the age of 60 and above the age of 80 tend to choose SLT more readily, experts point out. "It's about compliance," says Sanjay Asrani, MD, a professor of ophthalmology at Duke University in Durham, North Carolina. "Younger patients recognize that their busy schedules won't leave time for putting in drops, and older patients may have physical or memory limitations that impair their ability to instill or remember to instill the drops. They're also likely to be on multiple other medications, and are frequently happy not to add another."

Dr. Asrani says patients may get lulled into a false sense of security with SLT. "They should be counselled carefully before and after that this isn't a lifetime cure for glaucoma, but a time-limited treatment that still requires regular pressure monitoring."

Choosing A Lens

SLT lenses are designed to minimize laser beam distortion and provide good visualization of the angle. These clinicians say they've used the Latina SLT lens, Magna View gonio lens, Ritch laser trabeculoplasty lens (all from Ocular Instruments) and the SLT lenses from Volk.

"We use the Latina or Volk SLT lenses because they correct for astigmatism and maintain a circular laser beam profile so you can maintain laser spot size for accurate energy delivery to the TM," Dr. Bournias says. "SLT uses a 400-µm circular spot, and the large spot size (compared to ALT's 50-µm spot), coupled with any corneal astigmatism, can produce an oblong shape that won't have even energy distribution."

"The Latina lens has one mirror

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

In the treatment of Thyroid Eye Disease (TED),

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with TED, without concomitant steroids (vs placebo at Week 24).[2-4]

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

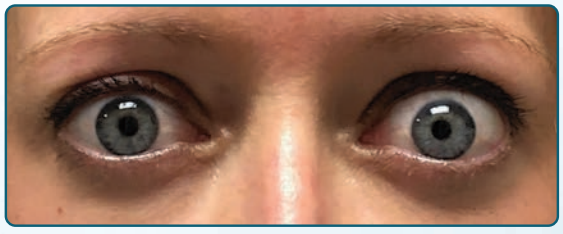
Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

TEPEZZA®
teprotumumab-trbw

TEPEZZA significantly decreased proptosis, one of the most disfiguring symptoms of TED[1,2,5,6]

SEE THE TEPEZZA DIFFERENCE[7*]



BASELINE
Proptosis: 19 mm OD, 20.5 mm OS

OD, oculus dexter; OS, oculus sinister.

WEEK 21: ON DAY OF 8TH INFUSION
Proptosis: 17 mm OD, 18 mm OS

*Real patient treated with TEPEZZA. Individual results may vary for patients treated with TEPEZZA.

Significantly greater proptosis responder rate† (Study 2)[1,2]

TEPEZZA
83%
TEPEZZA (n=41)

vs

Placebo
10%
Placebo (n=42)

P<0.001 at Week 24

†Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

» See more before and after photos

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on following page.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf. **5.** Data on File. Horizon, December 2019. **6.** Bruscolini A, Sacchetti M, La Cava M, et al. Quality of life and neuropsychiatric disorders in patients with Graves' orbitopathy: current concepts. *Autoimmun Rev*. 2018;17(7):639-643. **7.** Data on File. Horizon, December 2020.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia

b - Hyperglycemia includes blood glucose increase

c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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HORIZON

and the Ritch lens has two," Dr. Asrani notes. "I have to rotate the Ritch lens only once, whereas I rotate the Latina lens three times. The Latina lens has a smaller footprint, so it goes more easily into eyes with small palpebral fissures. I've been using this lens for a number of years."

Dr. Realini notes that using the Latina lens with the rotating flange enables him to spin the lens without having to release and re-grasp it. "I can do an entire 360-degree treatment all at once, without lens manipulation-related interruptions," he says.

Preoperative Preparation

After informed consent and instillation of a topical anesthetic, a pressure-lowering drop such as brimonidine is often instilled to reduce the risk of a post-laser pressure spike.

While some clinicians use miotics, Dr. Realini and Dr. Bournias say they don't. "In general, a miotic will pull the lens-iris-diaphragm forward, which might inhibit access to the TM," Dr. Bournias says. "The pupil contraction will also decrease the blood-aqueous barrier, which may lead to more inflammation."

Dr. Gazzard says mydriatics, too, are a no-go for him. "If a patient has been dilated for an exam, I do the laser on another day," he says. "Dilated pupils increase the risk of laser energy passing through the pupil, which can be damaging. I wouldn't expect that to happen, but it's a possibility."

Prior to performing SLT, a coupling agent must be applied to the ocular surface for visualization. "I use an artificial tear gel, rather than the typical gonioscopy coupling agent," Dr. Realini says. "It's the same chemical, but 1/10th the concentration, so it's far less viscous, and the lens rotates and comes off the eye more easily—it doesn't fall off the eye during the procedure, nor do I have any problems with bubbles. The artificial tear gel is perfectly adequate for maintaining coupling during the procedure."

Dr. Asrani says he uses Refresh Celluvisc preservative-free tears (Allergan) inside the well of the lens to prevent the patient's having blurry vision and stickiness at the end of the procedure. Typical coupling agents such as hydroxypropyl methylcellulose can be very sticky on the ocular surface; using artificial tears can avoid this and may also be gentler on the corneal epithelium.[3,4]

The Full Circle

Once the patient is brought to the laser, the lens is placed on the eye to provide a magnified view of the TM, where approximately 80 to 100 532-nm laser pulses are placed, evenly spaced, 360 degrees around the angle.

Today, most clinicians treat the full 360 degrees, rather than 180 degrees, as is standard with ALT. "With SLT, we tend to get better results with 360 degrees," says Dr. Bournias. "I try to get in about 90 to 100 spots. If the patient has PAS, I treat in-between the PAS, hoping the patient has at least 180 degrees of exposed TM."

"Several studies show that 360 degrees is superior to 180," Dr. Realini adds. "Why would we want to leave anything on the table when there's no cost to finishing the full treatment in one sitting?" He notes that he'll split the procedure into two 180-degree sessions about two weeks apart in heavily pigmented eyes at high risk for IOP spikes, such as patients with pigmentary glaucoma or those who've had complicated cataract surgery.

A version of the "energy technique," proposed by Mark Latina, MD, when he first described SLT in 2002 is widely used.[5] His original technique involved placing 50 spots over 180 degrees, at energy levels ranging from 0.4 to 1.4 mJ/pulse. Now, lasers are initially set at 0.8 mJ and increased or decreased in 0.1-mJ steps depending on changes in the cavitation bubbles.

"I start out at 0.8 mJ and increase or decrease the laser energy, depending upon the response," says Dr. Asrani. "I aim for at least half of my spots having a fine, champagne-bubble appearance. I do about 75 to 85 spots per eye and space them out by one or two spot distances. I don't start at any particular section of the angle, but when I treat the lower TM, which is reflected by the upper mirror, I typically have to lower the energy level because that area is more pigmented than other areas.

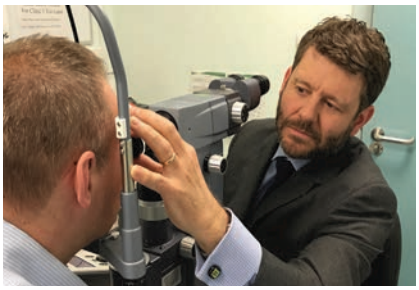
"If I'm doing SLT for the first time on a patient, I'll typically do one eye at a time, at separate visits," Dr. Asrani continues. "If I'm doing a repeat SLT, and I know the patient tolerated it very well last time, I'll do both eyes on the same day.

"The advantage of doing one eye at a time is that there are no limitations for the patient after the procedure," he continues. "They can go about their own daily activities without any restrictions, and they know what to expect when they come back for the other eye. When they come back I get a chance to see if the SLT was effective. It's like a monocular drug trial. Typically, I'll see a significant asymmetry of pressure, so I know the SLT works and that gives both the patient and me confidence enough to proceed with the second eye. SLT doesn't work about 10 percent of the time, and if it fails, then I don't do the other eye."

"I usually treat both eyes in the same sitting," Dr. Gazzard says. "I don't titrate the number of shots for different sized eyes, and I usually treat the whole 360 degrees of the TM with 100 pulses. I use a very low laser exposure, around 0.3 mJ for very pigmented angles, all the way up to 1.6 mJ in very unpigmented angles that need more laser to get a result. I'm looking for a just-visible formation of champagne bubbles at the TM."

Post Laser Care

Studies have suggested that anti-inflammatory drugs such as topical steroids and NSAIDs may help reduce the risk of post-laser pressure spikes, but Dr. Gazzard notes that such pressure spikes are rare. "They're much



Gus Gazzard, MD, sets up a patient for SLT.

less common than we thought when we first started using laser," he says. "I recheck pressure after 45 minutes. I haven't found that anti-inflammatory drugs help pressure response, though I do give patients an anti-inflammatory drug such as Ketorolac to use in case the eye is painful."

"I don't use any post-laser steroids or NSAIDs," Dr. Asrani says. "I've had good enough outcomes without them, so, I put in only one drop each of brimonidine and prednisolone at the end of the laser procedure. I check patients after 30 minutes, and if the pressure rises, I check again in 15 or 20 minutes. I've stopped doing one-week pressure check visits. After many years I've found almost no one has a pressure spike one week later, so now I see them back in five weeks."

"I also don't use any post-laser anti-inflammatory therapy," Dr. Realini says, who has likewise eliminated the one-week follow-up visit. "I haven't used any in 15 years and there have been no problems. We published data from a randomized clinical trial in the U.S. on the use of steroids versus no steroids and found no differences. In the West Indies Glaucoma Laser study (WIGLS), which I ran for many years, we looked at the course of inflammation postoperatively in AfroCaribbean eyes that received SLT and didn't receive any anti-inflammatory therapy. Inflammation postop was clinically insignificant. Of the thousands of patients I've treated with SLT, four have had a postop inflammatory reaction, which I subsequently treated with topical anti-inflammatory therapy. I think it's smarter to treat the four who need it than all those who don't. It's expensive and comes with the hassle of more drops."

Post laser complications with SLT are few, but there's a small chance you may encounter a scratch on the cornea from the SLT lens. "In high myopes, there's a very small but significant chance of corneal edema," Dr. Gazzard adds. "I've done hundreds of SLTs and have only seen it in three or four patients, but it does happen. Something about the optics of the anterior segment of very high myopes seems to be the problem. I don't think it's related to pigmentation in the front of the eye. It may be related to the path the laser takes through the corneal endothelium. Some patients may also get an endotheliitis that lasts a few days. If that happens, I normally treat with topical anti-inflammatories or mild steroids."

Follow-up

At the follow-up visit, clinicians check whether the patient had an IOP response. "IOP fluctuates a great deal from visit to visit," Dr. Realini says. "The AAO recently stopped recommending the monocular drug trial as a way to measure drug efficacy when starting new therapy because it's hard to tell on the first treatment whether or not it's working because of pressure fluctuations. The same goes when assessing SLT.

"If I see the patient back in one month and they haven't had the IOP response I was hoping for and they aren't in need of urgent pressure reduction (if they are, SLT isn't suitable), then I bring them back in another month to check pressures again," he says. "In most cases, eyes that haven't responded at one month respond at two months."

If patients have responded at the one-month mark, Dr. Realini says that's probably the IOP reduction you're going to get. "In WIGLS there wasn't any further reduction in mean IOP from one month to three months or twelve months. Our results have been replicated by several investigators in various African countries."

These results are consistent with other study findings concerning SLT's efficacy among different ethnicities. "The nice thing about SLT is that it works equally well in patients who are pigmented versus those with almost no pigment in the TM," Dr. Bournias says. "In my 1997 AAO presentation, I presented findings that showed ALT had significantly lower success rates in African-American patients than white patients at one year follow-up (52 versus 80 percent, $p<0.05$).[6] SLT demonstrates similar results in black and white patients." He says this is likely due to the thermal relaxation time of melanin in the TM, which is approximately 2 microseconds. SLT's 3-nanosecond pulse duration distributed over a 400-µm spot is too brief for melanin to transfer thermal energy. ALT is a 50-µm spot with 0.1-second constant-wave duration.

The LiGHT Trial also noted SLT's efficacy in a diverse population. It included a significant number of non-white individuals, including South Asians, African and AfroCaribbean people and a small number of East-Asian patients. "We didn't power the trial to look for differences among ethnicities, but we found no differences between whites and non-whites," Dr. Gazzard says.

Retreatment

"In the same eye, I'd do a repeat SLT treatment no earlier than 18 months," Dr. Asrani says. "If the effect wears out much sooner, the chances are the next one will wear out even sooner and it's not worth it. Typically, I've seen the effect last 18 to 36 months."

"I'll repeat primary SLT fairly quickly if patients are highly motivated to stay off drops," Dr. Realini says. "About 85 to 90 percent of patients respond well to first-line SLT. My impression is that about half of those who don't respond to first-line SLT will respond to a second treatment. If we pick up

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that half, we're looking at response rates in the 92- to 95-percent range with one or two SLTs. Albert Khouri, MD, published a paper that looked at whether response to the first SLT predicated response to a second SLT and found that there's not much connection. People who had a poor first SLT response can have a great second SLT response."

The LiGHT Trial also published a paper that found repeat SLT successful. "We showed that if the laser wore off within 18 months, repeating it seemed to be very powerful; it worked not only as well but for even longer than the first laser," Dr. Gazzard says. "We found that 60 percent of those patients were still controlled with laser alone after another 18 months of follow-up."

Dr. Bournias reports that his 2006 findings suggested SLT can be repeated up to three times. "Back then, people wondered if we could repeat SLT, since there are no thermal effects, like with ALT," he explains. "My study included 52 eyes treated with 360-degree SLT who had initial treatment success for at least one year. I found that 90 percent (47 eyes) had a successful repeat response maintained for at least one year and about 60 to 70 percent had another [third] response (*Figure 1*).

"When patients stop responding to SLT, I usually switch to ALT," he continues. "I've found those patients have a response. Likewise, those who don't respond to ALT often respond to SLT. You can do these treatments in any order you want; however, I recommend trying SLT first because of its lack of coagulative effect."

Dr. Realini is the chief investigator of the Clarifying the Optimal Application of SLT Therapy (COAST) Trial. Among the research team are Dr. Gazzard and Mark Latina, MD, the inventor of SLT. COAST is slated to enroll more than 600 patients at up to 20 centers around the world to compare standard SLT treatment to low-energy SLT and explore a low-energy SLT retreatment paradigm akin to treat-and-extend for anti-VEGF.

Pearls for Success

Here are some strategies to keep in mind when performing SLT:

• ***Trial a prostaglandin to rule out inflammatory glaucoma.*** "If they don't tolerate it, then it's very likely their glaucoma is related to inflammation," Dr. Asrani says. "I'm extremely hesitant to perform SLT on these patients because it can result in a massive fulminant rise of pressure. If they tolerate it, I offer them the choice of staying on the drug or doing SLT. Most choose SLT."

• ***Get comfortable.*** Though the SLT process is a short one, if you or the patient aren't comfortable, your accuracy with the laser may not be perfect, Dr. Asrani says.

• ***Identify angle structures correctly.*** "Learn compression gonioscopy to learn how to identify angle structures," Dr. Asrani advises. "Many times what we think is the TM turns out to be a pigmented Schwalbe's line or the ciliary body band. If you inadvertently laser the Schwalbe's line, there won't be too many downsides, except possible corneal edema, which is usually reversible. But if you inadvertently laser the ciliary body band, the eye will go into ciliary spasm and the refraction will change. The eye becomes very painful and severely inflamed, requiring prolonged steroid treatment. If you're not able to identify the TM, you won't know what you're lasering.

"It's important to target the TM correctly and perfectly, with an end-on spot," he continues. "By that, I mean that the laser beam should be focused perpendicularly to the TM. Angulate the lens to achieve this."

• ***Champagne bubbles.*** "Make sure you can see a bubble at least 50 percent of the time," Dr. Gazzard says. "Some people are cautious and undertreat. Some look for streams of bubbles on every pulse, and that's probably slight overtreatment." Large bubbles are another sign of overtreatment, which may result in scarring, he adds.

• ***Titrate the laser power.*** "Do this as you work your way around the eye," Dr. Gazzard says. "Angles vary tremendously in pigmentation, and what might be the right level of laser power for the heavily pigmented inferior angle may be insufficient for the superior angle."

• ***Ask patients with deep-set eyes to lean back.*** "It's not possible to use the upper lens mirror on these patients because you can't angle it up anymore—the brow bone limits your access," Dr. Asrani notes. "In those cases, I ask the patient to lean back from the slit lamp so I'm able to achieve laser treatment with the upper mirror area."

Special Considerations

In patients with traumatic glaucoma you may only be able to laser the nonaffected areas of the TM. "Be sure to avoid lasering the area of the angle recession that indicates TM damage," Dr. Asrani says.

"In phacomorphic angle closure patients, the lens is thick and occupies a lot of the anterior chamber and angle," he continues. "These patients typically have raised pressures. In these cases, low-power SLT (about 0.6 mJ) with compression and angulation of the lens is recommended because these TM cells are quite pigmented and often in constant contact with the iris.

"Pigmentary glaucoma and pseudoexfoliation glaucoma also require lower-power SLT," he adds. "These patients have a lot of pigment in the TM, which absorbs laser energy very quickly. Any higher powered SLT will result in a massive pressure spike." ◀

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THINKING OF TRYING MIGS? 10 QUESTIONS ANSWERED

Surgeons offer advice for getting started with MIGS and making the most of these surgeries.

CHRISTOPHER KENT
SENIOR EDITOR

With the popularity of minimally invasive glaucoma surgeries continuing to increase—and new MIGS options in the pipeline—more surgeons are adding one or two MIGS procedures to their toolbox every year. Here, surgeons with extensive experience performing these surgeries answer questions often asked by cataract surgeons thinking about going down this path.

1 Why offer MIGS?

Obviously a key reason to offer MIGS to an appropriate patient is the ability to lower IOP further than cataract surgery alone. However, surgeons point out several other advantages.

Vikas Chopra, MD, medical director of the Doheny Eye Centers Pasadena and a professor of ophthalmology at the David Geffen School of Medicine at UCLA, believes that every general ophthalmologist should have one or more MIGS in their armamentarium. "The majority of cataract surgeries in the United States are performed by comprehensive ophthalmologists, and many of their patients have mild to moderate glaucoma—the ideal population for MIGS," he notes. "One of the main advantages of MIGS is reduction in medication burden. This greatly enhances a patient's quality of life, and it's well-documented that adherence with glaucoma medications is a major issue, with consequences that can include glaucoma progression. In fact, we're increasingly seeing patients who've done research on the internet and want specific MIGS procedures done in conjunction with their cataract surgery."

Davinder S. Grover, MD, MPH, an attending surgeon and clinician at Glaucoma Associates of Texas in Dallas, points out that in addition to having smaller pupils and possibly some zonular weakness, patients who have both cataract and glaucoma are at a slightly greater risk of having a postop pressure spike. "In addition to lowering the patient's overall pressure and decreasing their dependence on drops, most MIGS procedures help to mitigate the potential for that postop pressure spike," he notes.

What about the increased surgical risk associated with adding a second procedure to cataract surgery? "Any time you add an additional step to surgery there's a very small chance of something going wrong," notes Arsham Sheybani, MD, an associate professor of ophthalmology and visual sciences at the School of Medicine at Washington University in St. Louis. "However, in the hands of an experienced surgeon, the risk of a minor complication is probably less than 5 percent. In terms of something serious like a cyclodialysis cleft, I'd say the risk is less than 1 percent. If the patient and the doctor decide that adding MIGS isn't worth it—maybe the doctor doesn't feel comfortable doing MIGS—then so be it. But I do think anyone doing cataract surgery on a patient who has glaucoma or is on glaucoma medications needs to inform the patient that these options exist."

Dr. Sheybani points out that with such a low risk associated with adding MIGS to cataract surgery, and potential upsides like reducing the

This article has no commercial sponsorship.

Dr. Sheybani has been a consultant for Allergan, Alcon, Santen, Katena and Ivantis. **Dr. Grover** is a consultant for Allergan, New World Medical, Olleyes, Reichert and Santen. **Dr. Chopra** reports no relevant financial ties to anything discussed in this article.

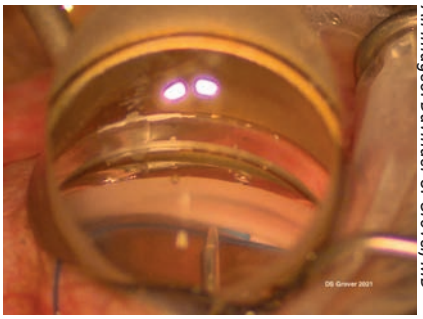
need for medications and reducing the likelihood of needing further surgery in the future, doctors who aren't already offering MIGS should be considering it. "It's certainly something that any cataract surgeon should be able to master," he notes. "I've worked with residents and fellows who've only done 10 or 20 cataract surgeries, and they get the hang of working in the angle despite much less phaco experience than a comprehensive ophthalmologist."

"Incorporating a MIGS procedure doesn't add significantly to the risks of the surgery, but it adds a lot of potential benefits," Dr. Grover concludes. "After all, you're already in the eye to remove the cataract. You could argue that if a patient only has very mild glaucoma, the cataract surgery alone might be sufficient; the iStent and Hydrus trials showed convincingly that cataract surgery does lower IOP a little bit. But I'd say that if a patient has mild to moderate glaucoma and is using multiple drops, it's a disservice to the patient not to do something more to address the glaucoma."

2 What skills will I need as a MIGS surgeon?

"If you're thinking about adding one of the MIGS angle surgeries to your armamentarium, the first thing you need to do is understand angle anatomy," notes Dr. Grover. "Also, you need to be familiar with gonioscopy—not just clinical gonioscopy, but intraoperative gonioscopy."

"One of the best ways to get started is to do gonioscopy in clinic," says Dr. Sheybani. "A lot of us who aren't glaucoma specialists aren't doing gonioscopy very often. As a result, we're not accustomed to visualizing the angle structures; sometimes the zones blend together. So the first big benefit of doing gonioscopy in clinic is that you'll start building your base understanding of what's normal and what's not. Once you get accustomed to doing gonioscopy in clinic, the next step is to start doing gonioscopy in the OR during some of your routine cases."



All images: Davinder S. Grover, MD

A 5-0 prolene-suture GATT. The blunted-tip suture has passed 360 degrees around the canal and will soon be retrieved and externalized to create a circumferential 360-degree *ab interno* trabeculotomy.

"After you put the lens in the bag, before you wash out any viscoelastic, tilt the head and scope and put a gonioprism on the eye and look at the angle anatomy," suggests Dr. Grover. "Make sure you can identify all of the landmarks. Then, put an instrument into the eye. Note the tactile feedback, so you understand what it feels like to have a tool working in the angle. This can take a little while to get used to."

"For many of the MIGS procedures, mastery of intraoperative gonioscopy is critical for success," agrees Dr. Chopra. "It's important to practice getting the best possible view of the angle. Practicing will help you in multiple ways. First, you'll learn to use the goniolens in your nondominant hand while managing the angle-based surgery with your dominant hand. Among other things, this will help you avoid creating corneal folds due to compression. Second, you'll learn how much to tilt the patient's head, versus how much to tilt the operating microscope.

"Third," he continues, "you'll get accustomed to filling the anterior chamber with the right amount of OVD. Overfilling can compress Schlemm's canal, making it difficult to cannulate or surgically open during a trabecular bypass procedure, while underfilling can allow the iris to bow forward and obscure a clear view of the iridocorneal angle. Fourth, you'll learn to avoid nicking the perilimbal vessels, which can cause bleeding and clouding up of the corneal tear film, making the view through the gonioprism challenging."

Dr. Chopra adds that it's important to do your homework. "I'd strongly encourage ophthalmologists considering adding a MIGS surgery to their repertoire to watch surgical videos of the procedure to help learn the technique," he says. "Work with industry reps to do personalized wet labs, and sign up for surgical wet-lab training at meetings like ASCRS and AAO. Talk to colleagues and glaucoma specialists to pick up learning tips and surgical pearls. Perhaps most important, to have a successful procedure you need to understand the surgical anatomy—especially in the iridocorneal angle. That's why achieving expertise in clinical and surgical gonioscopy is essential."

3 Which MIGS option should I learn first?

Dr. Grover says that once you've grown accustomed to the basic angle maneuvers and refreshed your familiarity with angle anatomy, you can try some type of angle surgery. "Pick one MIGS surgery and work with it; get comfortable with the technique," he suggests. "Become familiar with the way it changes things at the postop follow-up visit. Options with a slightly easier skill set would include a goniotomy or an iStent. Goniotomy is easy to start with; once you understand angle anatomy it's relatively straightforward and doesn't require a huge amount of manipulation in the eye.

"At first, I'd start with milder cases of glaucoma where you don't need a tremendous amount of pressure-lowering," he continues. "In those cases a goniotomy or iStent will be of benefit, and those procedures are relatively safe. Once you're comfortable with those, you can talk about trying options like the Hydrus, or performing a GATT. The second MIGS option you choose should

be based on the type of patients you generally treat, and how much pressure lowering is likely to be required."

"What you offer," Dr. Chopra adds, "should be based on your comfort level with learning the procedure, understanding how to manage its intraoperative and postoperative complications, and whether you have enough surgical volume to improve your experience beyond the learning-curve phase."

"I'm biased toward performing stenting procedures in general," says Dr. Sheybani. "However, I think if you're trying MIGS for the first time, doing something that doesn't leave a device in the eye might be a good way to go; that way, if you make an error you won't leave something permanent in the eye in the wrong spot. That's why I think goniotomy is a good way to start learning how to work in the angle."

Dr. Grover adds that most of the MIGS procedures aren't that hard to learn. "I do all of the MIGS procedures, and I didn't learn any of them in fellowship," he says. "I learned by doing, watching, teaching and collaborating with my partners. I never stop learning and trying new techniques in the OR. I find that those who stop learning in the OR have a more difficult time incorporating newer techniques and gaining new knowledge."

4 Should I offer more than one MIGS procedure?

"Having the ability to offer at least two different approaches—even if they're both angle-based MIGS—is important," says Dr. Chopra. "That makes it possible to customize surgery for each particular situation."

Dr. Sheybani agrees that it's good to offer more than one MIGS procedure, but notes that there's no need to offer them all. "If you're trying to treat a wide array of patients, it's good to become proficient at one stenting option, because that will give you the ability to treat patients who might, for example, not be able to stop taking blood-thinning medications," he explains. "Then, it's good to have a stripping or cutting option, just because that gives you the ability to treat a wider angle. It also means you'll have a stand-alone option that can be done separately from cataract surgery—with the caveat that if you're doing stand-alone MIGS, you probably need to get proficient at treating at least 180 degrees of the angle. The bottom line is, if you master one stripping option and one stenting option, you'll be able to cover a wide array of patients.

A goniotomy with the KDB Glide. Note the white stripe on the left side of the angle, demonstrating the treated angle structures with the exposed back wall of Schlemm's canal visible.

"Generally," Dr. Sheybani concludes, "if you're looking for safety and the patient is already controlled on medications, the disease is stable, the optic nerve and visual fields aren't getting worse and the patient needs cataract surgery, the stenting options are the way to go. If you're looking to reduce the number of medications or achieve significant pressure reduction at the time of cataract surgery, then you should really start considering either a larger stent or a larger stripping procedure."

5 What about options that don't involve angle surgery?

The MIGS angle surgeries are clearly the mainstay MIGS procedures for many surgeons, but there are other procedures that some surgeons (though not all) consider to be MIGS procedures. Three of the most notable are Allergan's XEN gel stent, a flexible *ab interno* collagen implant draining aqueous fluid into the subconjunctival space through a scleral channel; endoscopic cyclophotocoagulation (ECP), which uses a laser endoscope to visualize and ablate the ciliary body epithelium; and noninvasive micropulse transscleral cyclophotocoagulation.

"Options like the XEN are for surgeons treating more moderate-to-advanced glaucoma," notes Dr. Grover. "I actually consider XEN to be in a different category. It involves an entirely different skill set."

Dr. Sheybani says he also doesn't think of XEN as being a true MIGS procedure. "It's kind of a hybrid between MIGS and traditional surgeries," he says. "It's also kind of a hybrid between a tube shunt and trabeculectomy surgery. You could call it a MIBS—minimally invasive bleb surgery. It can potentially get your pressure down a bit lower, so there's a broader patient population that can be treated. But it's not a MIGS surgery that uses the physiologic outflow pathway."

Dr. Grover says that he doesn't perform ECP very often, but sees it as a reasonable option in some situations. "ECP involves a different skill set, although it doesn't have a huge learning curve," he notes. "Mostly, I avoid using ECP as the sole treatment. The eye has a faucet and a drain; it makes aqueous and drains aqueous. If your drain is clogged and you're not doing anything to enhance outflow, the sink is going to overflow whether the faucet is turned on completely or halfway. Typically, I find that ECP works for me when outflow is already established, or doing ECP in combination with an outflow-enhancing procedure. I don't believe ECP done by itself provides a significant benefit in most cases, unless you have an intact outflow pathway.

"Some surgeons do combine an angle surgery with ECP—a combination inflow and outflow procedure," he notes. "I don't do that, but I don't think there's anything wrong

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with it, per se. The reason I choose to avoid it is that ECP increases the rate of inflammation, and we don't really know how inflammation affects wound healing in the angle. However, some surgeons do combine angle surgery and ECP, and they report relatively good results."

Dr. Sheybani says that, like the XEN, he doesn't think of ECP as a true MIGS procedure. "Many of us use it more in angle closure and plateau iris cases," he explains. "A patient with a functioning tube shunt who needs a little bit more pressure reduction could be another good choice. And I do appreciate the endoscopic aspect for viewing structures during anterior segment surgeries if there's a lens dislocation, or if the patient has a problem that requires viewing the ciliary body. But it's a totally different ball game from most MIGS as far as the structure you're treating."

Dr. Chopra says his experience with micropulse transscleral cyclophotocoagulation has been positive. "This procedure has been quite effective and well-tolerated in patients for whom a non-incisional surgery makes sense, either as a primary or adjunctive procedure," he explains.

Dr. Grover believes that micropulse technology has a lot of potential, but is still somewhat problematic. "The issue is that people are still trying to figure out the settings that will produce the most predictable outcomes," he explains. "I don't think this is the fault of the technology itself; we need to better understand the parameters that are needed to treat different patients. Many groups, including ours, are working on this."

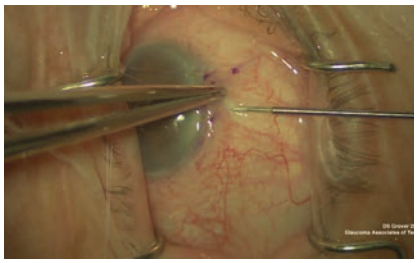
6 What about the suprachoroidal space?

Shunting aqueous into the suprachoroidal space is another approach to lowering pressure that's shown promise. Surgeons briefly had access to the CyPass stent, designed to do this, but it was withdrawn from the market after some patients experienced corneal endothelial cell loss. However, new options designed to tap into the suprachoroidal space, including the iStent Supra, are now in the pipeline.

Dr. Grover believes that such an option could be very useful. "It's probably not necessary for patients with mild glaucoma, but it could be essential for patients with refractory glaucoma and a lot of scarred conjunctiva," he says. "I believe the concern here is the risk-benefit ratio. I suspect that the CyPass ended up being withdrawn because they were targeting patients with mild glaucoma who were not likely to go blind, and the risks—assuming that the endothelial cell loss was actually real—turned out to be too great for the benefits a mild glaucoma patient might gain. On the other hand, if a patient has serious disease and will go blind if their glaucoma isn't addressed, then considering a slightly more invasive procedure that might cause mild endothelial cell damage is potentially justifiable.

"I think being able to access the suprachoroidal space will be a very valuable means of treatment once we have an approved device," he concludes. "This approach has a lot of potential, and I think it will be one of the next frontiers."

Dr. Sheybani's outlook is a little more cautious. "I believe a shunt into the suprachoroidal space could be a good option for a refractory patient," he says. "But until we figure out how to prevent scarring that leads to sudden failure, how to prevent the hypotony that rarely occurs, and how to prevent the effusion that can cause shallowing of the anterior chamber, it's not something I'd add to cataract surgery for a patient with mild disease. I think it would be reasonable to consider for a patient who might need something more than a trabecular-based surgery, someone who isn't a good candidate for subconjunctival surgery. And it might be good for someone who



Intraoperative photo demonstrating the *ab externo* closed conjunctival XEN implantation technique.

has failed prior procedures. But given the traditional view of cataract surgery plus a MIGS procedure to address mild glaucoma, I wouldn't jump to the suprachoroidal space, at least using the current technologies that are coming down the pike."

7 Which MIGS should I offer to which patients?

Although he acknowledges that a choice of MIGS procedure should be customized for each individual patient, Dr. Chopra believes it's a good idea to try to enhance the patient's own outflow system before trying to bypass it. "I tend to recommend trabecular meshwork bypass procedures as first-line, especially in patients with mild to moderate glaucoma and/or a desire to reduce their topical medication burden," he says.

"For other patients with more advanced disease who may require a very low intraocular pressure, I routinely offer the XEN gel stent," he continues. "The XEN generally achieves low IOPs approaching those achieved with traditional glaucoma procedures like trabeculectomy or tube shunts—although it may leave the patient with a greater medication burden [than those procedures].

"Occasionally you may encounter an older, monocular patient who may not be a good surgical candidate due to systemic or ocular health issues," he adds. "In that case it would make sense to consider starting with a non-incisional procedure like micropulse transscleral cyclophotocoagulation."

Dr. Grover notes that when combining MIGS with cataract surgery, the characteristics of the cataract shouldn't make too much difference in terms of which MIGS you choose. "In general, the angle anatomy needs to be normal, appropriate and visible," he says. "If a patient has a very small eye or narrow angle, that can complicate things."

8 Which patients shouldn't be offered MIGS?

Dr. Sheybani says there are cases in which he might not add a MIGS procedure to cataract surgery. "If the patient is an ocular hypertensive with a 0.4 disc, a TMax pressure of 22 or 23 mmHg and no disc or field changes—but someone has started them on a prostaglandin—I'd say cataract surgery alone for that patient is perfectly fine," he explains. "But in that case I'd wonder whether the patient really needs the prostaglandin.

"The data from the Ocular Hypertension Treatment Study suggests that when there's low suspicion of glaucoma but elevated IOP, the end result is the same even if you wait to start medications," he continues. "If the patient may not really need the drop, then you probably don't need a MIGS procedure either. But if the patient has disc changes and is on a medication, even if the pressure is controlled, then a MIGS procedure is very reasonable. Or if you think that someone with a healthy disc is at high risk of progressing, that's another good MIGS candidate."

Dr. Chopra agrees that not every patient should have a MIGS procedure. "The decision about adding MIGS has to be individualized, but it should certainly be dictated by the patient's level of glaucoma, as well as the patient's ability to tolerate topical anti-glaucoma medications," he says. "In any case, proper preoperative screening with in-office gonioscopy, and a detailed ocular exam to determine feasibility of surgery based on ocular anatomy, are essential for properly matching a particular patient to a specific procedure.

"A patient shouldn't have MIGS just because it's the newest addendum to cataract surgery," he adds. "In the randomized, controlled trials for FDA approval of all the trabecular bypass procedures, cataract surgery without MIGS was also effective in achieving lower intraocular pressures in a majority of patients. So if the patient isn't an appropriate candidate for a MIGS procedure, or the ophthalmologist isn't comfortable with a procedure, the patient should just undergo the cataract surgery."

9 What should be done before a MIGS surgery?

Surgeons offer these suggestions:

• ***Make sure MIGS is mentioned in your pre-cataract-surgery informed consent.*** "When you're doing cataract surgery on a patient with a diagnosis of glaucoma, even if the pressure is controlled—especially if the patient is on medication treatment—MIGS should at least be mentioned in the informed consent," says Dr. Sheybani. "The patient should be made aware that there are procedures with a favorable safety profile that can be done at the same time as cataract surgery that could potentially reduce the need for medications after surgery and decrease the need for later glaucoma surgery. You have to tell the patient about all the major options that exist—including toric lenses and multifocals—whether you offer them or not. Then, it's up to you and the patient to decide whether to add a MIGS procedure."

• ***Don't offer a procedure you seldom perform.*** "Ophthalmologists have an ethical obligation to offer only those MIGS procedures for which they're 'certified,' ones they're comfortable performing," says Dr. Chopra. "If you're only performing these procedures once in a while, it'll be challenging to

(Continued on p. 62)

Optimizing OCT Imaging

By Jose Antonio Mendoza, MD, MSc

Imaging technologies play an important role in our profession. The ability to visualize tissue and evidence of disease in detail is one of the cornerstones of our jobs, and it's important that our diagnostic technology gives us the highest quality information. High-quality images contribute to a more confident diagnosis, and ultimately better patient outcomes through more informed disease management. Advancements in Optical Coherence Tomography (OCT) imaging devices yielding such optimized images were the topic of a workshop featured at the **virtual eyeRISE 2021 conference**.

When considering OCT imaging devices, the quality can be affected by three parameters: 1) the scan area (field of view); 2) the scan density (resolution); and 3) the scan time. If we hold any one of these parameters constant, the other two factors can be inversely affected. Inherently, there has always been a need to make some tradeoff when selecting the scan pattern on our OCTs—until now.

In an effort to eliminate the need for eye care providers to have to choose between scan area and scan quality, Topcon Healthcare (Tokyo, Japan) developed PixelSmart™ technology for the Triton, Topcon's Swept Source OCT (SS-OCT) platform. At its core, PixelSmart is designed to deliver the best of both worlds—the image quality of a high-density line scan and the wide coverage of a dense cube scan—without sacrificing scan speed.

PixelSmart's new image processing algorithm is elevating visualization of the retina by delivering the clarity of averaged images throughout the entire volume scan—reducing speckle noise and improving contrast. The technology is a post-processing technique, meaning scan time is not affected and existing Triton scans previously captured on the device can be reprocessed to further enhance their scan quality.

This step forward in OCT imaging aims to provide clinicians with the highest possible image quality to help them better identify and differentiate between pathologies, with the goal of improving patient care and outcomes.

The following discussion reveals the positive first impressions from Jose Mendoza, MD (Lima, Peru), an ophthalmologist who spent several months evaluating PixelSmart technology on his patient population.

OCT in Clinical Practice

What is your typical imaging protocol in clinic?
Dr. Mendoza: The protocol that I use the most on every patient is the 12x9mm 3D Wide scan, which gives me a lot of information about the macula and optic disc so I can pinpoint retinal and glaucomatous defects. If I need to focus on a smaller lesion, then I do an averaged line scan to get even more detail.

What percentage of your patients have cataracts and how is SS-OCT technology impacting your care of these patients?
Dr. Mendoza: Fifty percent or more of our patients have dense cataracts. These patients frequently also have glaucoma, AMD, or other retinal diseases in addition to their cataracts. Due to the longer wavelength and deeper penetration of SS-OCT technology, we can significantly improve our workflow because we can visualize the retina through opaque media and avoid surprises after surgery. For us, it's been a game changer.

How do you think improvements to B-scan image quality, with regard to en face and 3D structural visualization, help in the evaluation of retinal pathologies?
Dr. Mendoza: Sometimes rare diseases mimic other diseases and can be very difficult to differentiate. En face imaging can help the clinician decide between, for example, choroidal polyps and CNV, because it reveals a number of biomarkers that can't be seen on a single B-scan. 3D reconstruction is a great weapon to show the patient what is going on in their eye. Patients don't necessarily know what an RPE or CNV is, but seeing a 3D visualization can help them to better understand their condition.

By introducing PixelSmart have you been able to create a standardized scan protocol that covers most, if not all, of your imaging needs in clinic?
Dr. Mendoza: Yes, we have. We were using a lot of 3D imaging processing with en face visualization, but it was too time consuming to look through all of these patient findings and take advantage of all that the technology offers. By introducing a standardized screening protocol that incorporates a PixelSmart scan, we have been able to improve our clinical workflow. We've found that PixelSmart not only improves the quality of the scans but the time that it takes us to interpret the images.

Applying PixelSmart to Patient Cases

CASE STUDY 1: Vitreomacular Traction: Improving Upon 2D Imaging With PixelSmart

This vitreomacular traction case demonstrates how PixelSmart technology has greatly improved on 2D imaging. This 80-year old female, pseudophakic in both eyes since 2010, presented with complaints of blurred vision OU for two weeks. BCVA was 20/100 OD and 20/80 OS, and no other relevant pathologies were found on the physical exam. We performed simultaneous, pinpoint registered OCT and color fundus photography with the Triton SS-OCT.

In Figure 1, the fundus photograph for both eyes is unaffected by media opacities because the patient is pseudophakic, OU.

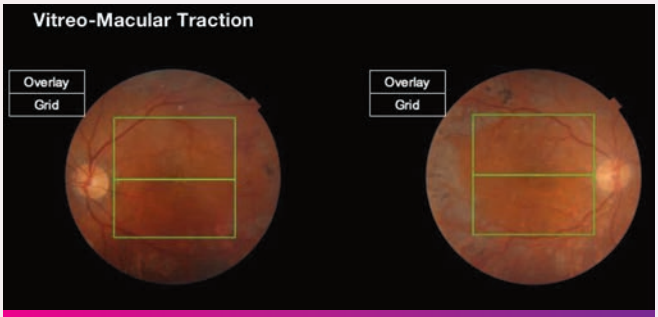


Figure 1.

Figure 2 shows vitreomacular traction with PixelSmart off. The surface of the retina reveals small hyperreflective bands that suggest an epiretinal membrane, but could be a reflection or an artifact.

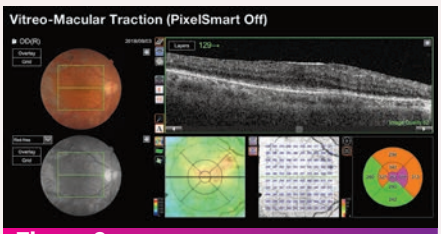


Figure 2.

In Figure 3, with PixelSmart on, the hyperreflective band can be seen clearly in the center of the fovea. It's also possible to see the extent of the vitreomacular traction—extending superiorly and nasally to the fovea.

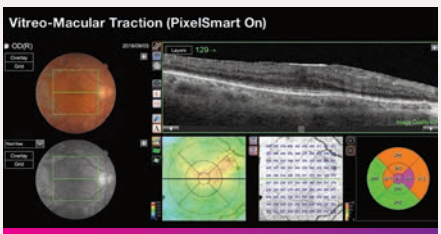


Figure 3.

In Figure 4, switching to en face imaging with PixelSmart off (left Panel A), the extent of the macular traction and the epiretinal membrane is apparent, but details are hard to see. When PixelSmart is turned on (right Panel B), details become clear across the epiretinal membrane, and some of the bands of traction and their locations in the surface irregularities can be visualized.

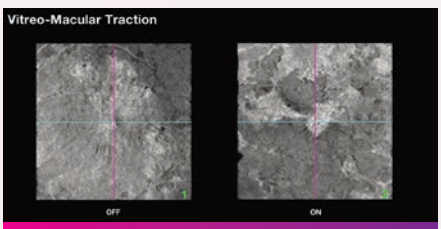


Figure 4.

Figure 5 depicts a 3D reconstruction using PixelSmart technology. The software not only corrects motion artifacts that frequently confound OCT images, but it also improves the 3D reconstruction of the image.

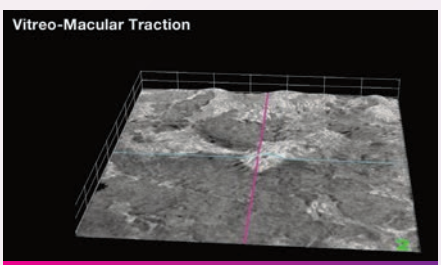


Figure 5.

In addition to high-resolution B-scans, the Triton can also create a movie of several different B-scans overlapping in full resolution. This type of visualization is very valuable when evaluating difficult cases.

CASE STUDY 2: Differentiating AMD from PCV: Cutting Through Opacities with PixelSmart

In this case, there is a need to differentiate between a neovascular membrane and polypoidal choroidal vasculopathy (PCV)—a pathology that can be the cause of exudative maculopathy, especially in Asian populations. PCV often gets misdiagnosed as macular degeneration due to similarities in the pathologies, which consequently impacts the effectiveness of the treatment. PCV can exhibit characteristic features on OCT that we can look for to distinguish its presence.

This 86-year old male, pseudophakic in the right eye with a previous diagnosis of bilateral AMD, presented with complaints of blurred vision in the left eye prior to cataract surgery. His BCVA was 20/40 OD and 20/100 OS, and no other relevant pathologies were reported. Using the Triton SS-OCT, the patient had OCT imaging and color fundus photography simultaneously captured, and ICGA was performed on another device.

In Figure 1, the patient's initial imaging revealed a dense cataract in the left eye, so SS-OCT technology was needed to image through the opacities.

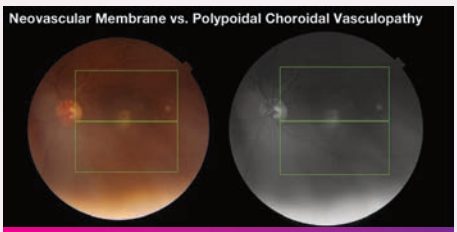


Figure 1.

In Figure 2, the patient's OCT image without PixelSmart is depicted. Usually with PCV, some polypoidal lesions and pigmented epithelium detachments are present, and the choroid appears thickened. The condition, in the spectrum of pachychoroid diseases, commonly exhibits a double layer sign which can be hard to visualize with a 3D volumetric scan, especially if the scan is not densely sampled.

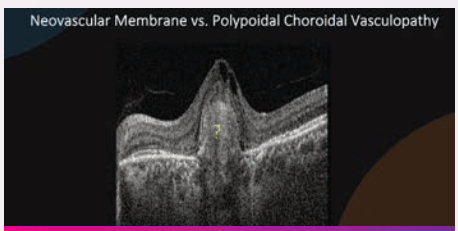


Figure 2.

Figure 3 is the resulting patient image after PixelSmart technology was applied, which enhanced the visibility of the lesions leading to the ability to make a more confident diagnosis.

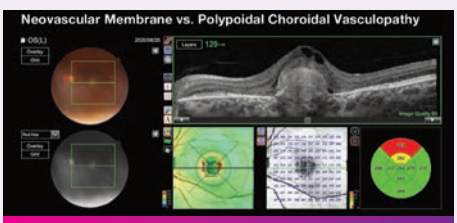


Figure 3.

In Figure 4, the B-scan illuminates hyperreflective foci, neovascular lesions, subretinal hyperreflective material, and pachychoroid. This is suggestive of classic AMD with neovascular membrane, rather than PCV.

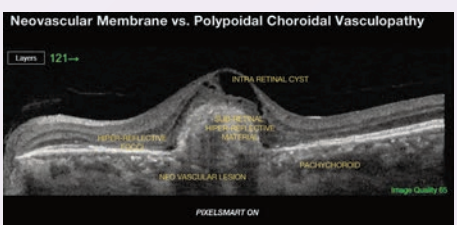


Figure 4.

As a clinician who depends on high image quality to make accurate diagnoses and treatment plans, the Triton SS-OCT with PixelSmart is invaluable technology that I've incorporated in my daily clinical practice. ●

Jose Antonio Mendoza, MD, MSc, is a practicing ophthalmologist at Ophthalmasalud Eye Institute and the Medical Director at CEDO Eye Diagnostic Center in Lima, Peru.

DRY EYE: WHAT'S IN THE PIPELINE?

Promising new treatments are on the horizon.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

The incidence of dry eye has been on the rise in recent years, and the pandemic has furthered the problem. "Screen time is increased when people are working from home and are on computers all day, as opposed to being in an office where they are walking around, talking to people and going to meetings," says Christopher J. Rapuano, MD, chief of Wills Eye Hospital's Cornea Service. "It's well-known that screen use increases dry-eye symptoms. Masks can also contribute to dry eye for a lot of people."

Fortunately, researchers are looking at new ways to treat the condition. Here's a look at some of the drugs and devices in the pipeline.

Reproxalap

Reproxalap (Aldeyra), a promising new agent, is a small-molecule reactive aldehyde species (RASP) inhibitor that covalently binds free aldehydes and diminishes excessive RASP levels.

In a recent study, reproxalap demonstrated rapid, broad and clinically relevant symptomatic control in dry-eye patients over 12 weeks of therapy.[1] Additionally, there was statistically significant improvement compared to vehicle in signs of dry-eye disease, as demonstrated by fluorescein staining. The results represent the first vehicle-controlled evidence for the therapeutic potential of RASP inhibition to ameliorate the signs and symptoms of dry-eye disease.

"RASP inhibition provides a novel mechanism of action that appears to have steroid-like efficacy and tolerability, without steroid side effects," notes John Sheppard, MD, practicing with Virginia Eye Consultants and CVP Partners, and serving as professor of ophthalmology at Eastern Virginia Medical School in Norfolk.

RGN-259

RGN-259 (RegeneRx) is a Tβ4-based sterile and preservative-free eye drop that's designed to be a novel treatment for dry eye and neurotrophic keratitis. Recently, the ARISE-3 Phase III clinical trial evaluating RGN-259 eye drops for the treatment of dry eye didn't meet its primary outcome measures, according to the company. However, researchers noted statistically significant improvement in ocular grittiness at one and two weeks after treatment, and post-exposure in a controlled adverse environment after two weeks of treatment with the drug, compared to placebo. Additionally, they say RGN-259 continued to demonstrate safety in the treatment of dry eye consistent with previous clinical trials.

Visomitin

Visomitin (Mitotech) is an eye-drop formulation of the drug SkQ1 that's been developed to target ophthalmic disorders like dry eye, uveitis and macular degeneration.

The company says that SkQ1 was designed to address dry eye through a novel mechanism of action that consists of acting on the mitochondria at a cellular level. It belongs to the class of cardiolipin peroxidation inhibitors developed for the treatment of several age-related disor-

This article has no commercial sponsorship.

Dr. Rapuano is a consultant for TearLab and Oyster Point. Dr. Pflugfelder is a consultant for Oyster Point. Dr. Sheppard is a consultant for Abbvie, Allergan, Aldeyra, Bausch & Lomb, LacriSciences, Mitotech, Novartis, Novaliq, Oyster Point, Quidel, Sun Pharma and TearLab. He has equity interest in LacriSciences, Oyster Point and TearLab.

ders, including dry eye. In contrast to current standards of care, which act primarily as anti-inflammatory agents, Mitotech says that SkQ1 has been shown to not only relieve inflammation but also to mitigate tissue degeneration and improve tear quality deficit by targeting oxidative stress within the eye. VISTA-1, a Phase IIb/III clinical study in the United States (NCT03764735), found that SkQ1 showed evidence of efficacy in reducing both the signs and symptoms in dry-eye subjects.

Mitotech and Essex Bio-Technology recently announced completion of enrollment in a pivotal Phase III VISTA-2 study of SkQ1 ophthalmic solution in patients with moderate to severe dry eye.

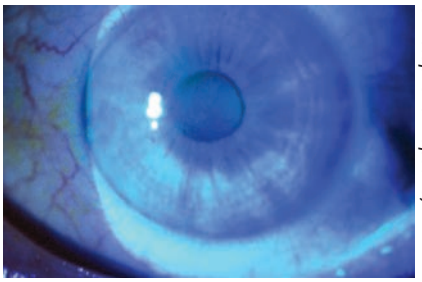
VISTA-2 is a multicenter, randomized, double-blind, placebo-controlled clinical study with two treatment arms, one receiving SkQ1 and one receiving vehicle administered twice daily. The study includes 610 patients in multiple centers across the United States who will receive treatment over a two-month period.

VISTA-2 was designed to confirm the outcome of VISTA-1.

OC-01

OC-01 (Oyster Point Pharmaceuticals) is a highly selective nicotinic acetylcholine receptor (nAChR) agonist being developed as a preservative-free nasal spray to treat the signs and symptoms of dry eye. The company says the drug's novel mechanism of action activates the trigeminal parasympathetic pathway in the nasal cavity to stimulate natural tear-film production.

Oyster Point says the Phase III ONSET-2 clinical trial yielded positive top-line results. This multicenter, randomized, double-masked, vehicle-controlled clinical trial included 758 subjects at 22 centers in the United States and investigated two doses of OC-01 nasal spray (0.6 mg/mL and 1.2 mg/mL), as compared to control (vehicle) nasal spray. Subjects were administered OC-01 nasal spray b.i.d. for four weeks.



Christopher J. Rapuano, MD

Mild diffuse superficial punctate keratopathy in a patient with moderate dry-eye syndrome.

Both tested doses of OC-01 showed a statistically significant improvement, with subjects gaining 10 mm or more in Schirmer's score at week four when compared to control. The percentage of patients gaining 10 mm or more on the Schirmer's test was 44 percent in the 0.6 mg/mL dose group, 47 percent in the 1.2 mg/mL dose group, and 26 percent in the control group.

Additionally, there was a statistically significant improvement in mean change in Schirmer's score at week four in both doses tested when compared to control.

Stephen Pflugfelder, MD, from the Baylor College of Medicine in Houston, believes that this product may be the next one to reach the market. "It's shown significantly greater increase in its endpoint of increased tear production," he says. "It offers a different approach, where it can provide an on-demand increase in tear production by using the nasal spray."

He says that he's excited about this drug, which appears to have a good safety profile. "It's the same medicine that's used in Chantix, which is a medicine people take to stop smoking," he says. "Oyster Point discovered that this drug can stimulate receptors in the nasal cavity and increase tear production. So, if the drug has the same efficacy as in the clinical trial, that's probably the drug I'm most excited about because it's a different mechanism of action and a different approach."

Nov03

NOV03 (Bausch + Lomb) is an investigational, proprietary, water-free and preservative-free solution, based on patented EyeSol technology from Novaliq GmbH.

The GOBI trial is the first Phase III trial evaluating the investigational drug NOV03 (perfluorohexyloctane) as a first-in-class eye drop with a novel mechanism of action to treat the signs and symptoms of dry-eye disease associated with meibomian gland dysfunction.

The GOBI trial included results from 597 participants aged 18 years and older who were randomized to receive either treatment with NOV03 or administration of placebo four times daily. The multicenter, randomized, double-masked, saline-controlled Phase III study was conducted at 26 locations in the United States.

NOV03 was well-tolerated, with the incidence of instillation site reactions below 0.5 percent. No treatment-emergent adverse events were reported by more than 2 percent of subjects in either treatment group.

"This product will most certainly make it to market," Dr. Sheppard opines. "It has a unique vehicle that's water-free, so it doesn't need a preservative. It's not metabolized, so any excess simply drains into the nasolacrimal system without systemic absorption. Because of its polymeric molecular nature, the drop is 20-µL instead of 50 like a regular solution or suspension drop. The cul-de-sac tear lake will only hold about 20 to 30 µL of volume, so its 20-µL volume is perfectly suited to the volume of the ocular surface. As a long-chain semifluorinated alkane, it has a direct stabilization effect on the meibomian glands, and then it solu-

bilizes the meibomian lipid secretions from the outside in and has an inherent anti-inflammatory effect."

CyclASol

CyclASol is a topical anti-inflammatory and immunomodulating ophthalmic solution, containing 0.1% cyclosporine A in EyeSol, developed for the treatment of dry-eye disease. The unique water-free drug product is based on the EyeSol enhanced ocular bioavailability technology that allows for several-fold higher corneal penetration of cyclosporine A in comparison to water or oil-based formulations. The previous Phase IIb/III trial (ESSENCE-1) evaluated the efficacy, safety, and tolerability of CyclASol in patients with dry eye.[2] In that study, CyclASol demonstrated statistically significant improvements in pre-specified endpoints for both signs and symptoms of dry eye when compared to its vehicle after four weeks.

The ongoing ESSENCE-2 trial is a multicenter, randomized, double-masked, vehicle-controlled clinical trial assessing efficacy, safety and tolerability of CyclASol for the treatment of signs and symptoms of dry eye. Positive results from ESSENCE-2 will allow for a New Drug Application filing to the US FDA in 2022, according to the company.

"The folks at Novaliq have shown that this shorter-chain semi-fluorinated alkane vehicle produces an excellent solubilization of the medication and allows it to remain on the ocular surface for an extended period of time to optimize absorption into the ocular surface tissues and the lacrimal gland," Dr. Sheppard says. "Again, the outstanding feature of this particular vehicle is that it's extremely well-tolerated. The self-discontinuation rate is well below 3 percent, and the side effects of stinging, burning and blurring are essentially equivalent to vehicle. This [patient comfort] sets it apart from other preparations—at least in the trials. The real world, though, is always full of surprises."

Lacripep

Lacripep (Tear Solutions) is a first-in-class topical synthetic peptide treatment for dry eye. It's a synthetic tear protein fragment of Lacritin, which is a nanomolar concentration constituent of normal human tears, but is lacking in the tears of dry-eye patients.

Preliminary outcomes of a Phase I/II trial of Lacripep in primary Sjögren's syndrome patients were recently released. The trial was designed to test proof-of-concept and optimize the design for the next planned study. Two strengths of Lacripep were tested. The lower-strength agent exhibited a highly statistically significant reduction in inferior corneal staining, as well as a statistically significant improvement in burning and stinging.

"This biologic medication accurately molecularly mimics Lacritin," Dr. Sheppard notes. "Lacritin is present in all eyes, but it's decreased in dry eye. Because of proof-of-concept in a meticulous Phase II trial, we're encouraged that Lacripep will have much broader applicability for less-severe dry eye or less-advanced surface disease."

EFC843

Novartis is studying a biologic lubricant found in synovial fluid, ECF843. The agent is a recombinant human lubricin (boundary lubricant) and an investigational compound. Efficacy and safety of ECF843 have yet to be established.

HBM9036

Tanfanercept (HBM9036, Harbour BioMed) is a modified 19-kDa TNF receptor 1 fragment. The drug is molecularly engineered as a therapy for relief of the signs and symptoms of dry eye. It was specifically developed for ophthalmic topical use with good surface permeability, strong TNF-α neutralizing activity, high stability and minor side effects, according to Harbour BioMed.

AR-15512

Aerie's TRPM8 agonist recently completed enrollment of its Phase IIb clinical trial. The company says that, when activated, the TRPM8 receptor may increase tear production and produce a cooling sensation to decrease discomfort.

AZR-MD-001

This drug, from Azura Ophthalmics, is in Phase II trials for the treatment of MGD. Azura says the new agent met its primary endpoints, showing improvements in signs and symptoms of MGD, reaching statistical significance when compared to controls.

TP-03

Tarsus' TP-03 is currently in Phase IIb/III trials for *Demodex* blepharitis, but is also in early trials as a dry-eye treatment. The company says the agent is designed to paralyze and eradicate mites and other parasites, and was well-tolerated in initial trials.

SURF-200

Surface Ophthalmics' agent recently entered Phase II trials for acute dry eye. SURF-200 is 2% betamethasone in the company's Klarity vehicle. It'll be studied in two different low-concentration formulations in 120 to 140 patients.

Though the dry-eye field is already filled with options for patients and their physicians, clinicians are always willing to give a new method a try. "Many patients just don't do well with the current treatments for dry eye," Dr. Rapuano says, "so it's exciting to see so many new products in development." ◀

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2. Sheppard, JD, Wirta DL, McLaurin E, et al. A water-free 0.1% cyclosporine A solution for treatment of dry eye disease. Results of the randomized Phase 2B/3 ESSENCE study. Cornea 2021. doi: 10.1097/ICO.0000000000002633. Epub ahead of print. Accessed Feb. 1, 2021.

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

OP-COM-000101

MANAGING TOP CATARACT SURGERY CHALLENGES

Experts review tough cases and how to manage them successfully.

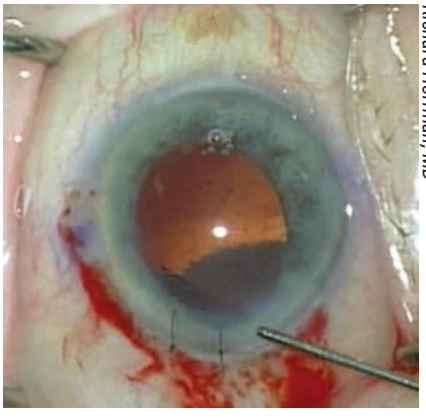
SEAN MCKINNEY
SENIOR EDITOR

As a surgeon, you're likely all too familiar with the many things that can go wrong when implanting IOLs, ranging from lens dislocations to posterior capsular tears. This month, experts offer insights on how to respond confidently to four major challenges that can catch surgeons off guard, potentially leading to significant complications and setbacks. Read on to gain insights on intraoperative zonular weakness or loss, a sudden flat chamber and firm eye, a broken capsule with a lost nucleus and wound burn.

When Zonules Fail

You're working on an eye and you realize that many clock hours are gone or weak. How do you respond?

"If the lens is stable and in good position, you may just want to leave it the way it is," says Mark Kontos, MD, a senior partner at Empire Eye Physicians, with offices in eastern Washington and northern Idaho. "Watch it carefully until you're assured that the stability will endure. If you've noticed this issue when there are still significant steps left to be taken in the surgery, then, yes, it will have a significant impact, especially if you still have most of the lens in the bag."



Richard Hoffman, MD

Figure 1. An early choroidal hemorrhage like this one would require an immediate termination of cataract surgery and referral to a retinal specialist.

If possible, Dr. Kontos tries to remove all the cortical material that isn't in the area of zonular loss. "Sometimes, I'll switch to a two-piece I/A, which is gentler on the eye and the bag," he notes. "If I determine that I shouldn't mess with the cortex, I'll try to create some structure in the area, perhaps with a capsular tension ring or three-piece IOL. Then I remove the remaining cortex once those structures are in place, providing the support I need."

In more serious cases, such as a loss of five clock hours of zonules or more, Dr. Kontos may turn to a Cionni ring. "You just have to be ready to adjust your technique, but you should always put the least amount of stress on the capsular bag that you can, to avoid losing the bag altogether."

Proceed with Caution

If he detects mild zonular weakness during a procedure, Richard Hoffman, MD, continues with the case. "You can usually get through it by delicately performing your hydrodissection and rotating the lens carefully, using a two-handed rotation," says Dr. Hoffman, clinical associate professor of ophthalmology at Oregon Health and Science University and a private practitioner at Drs. Fine, Hoffman, & Sims

This article has no commercial sponsorship.

Dr. Kontos is a consultant for Zeiss, Sun, Allergan and Johnson & Johnson Vision. **Dr. Hoffman** is a consultant for Microsurgical Technologies. **Drs. Mamalis** and **Kershner** report no relationships with companies that make products mentioned in this article.

in Eugene, Oregon. "If you're a divide-and-conquer surgeon, you can use a chopping method that puts less stress on the zonules."

When dealing with a dense lens, Dr. Hoffman is inclined to place capsular hooks, especially when the zonular weakness is extensive.

"You can use either localized zonular capsule hooks in an area of frank zonular loss or, if you have generalized zonular weakness or loss, you can use four capsule hooks around the periphery of the capsule, providing equal support of the lens," Dr. Hoffman says. He also uses the hooks prophylactically before surgery to avoid zonular tears, or dehiscence in patients who have known pseudoexfoliation, zonular weakness or, in some cases, very dense cataracts.

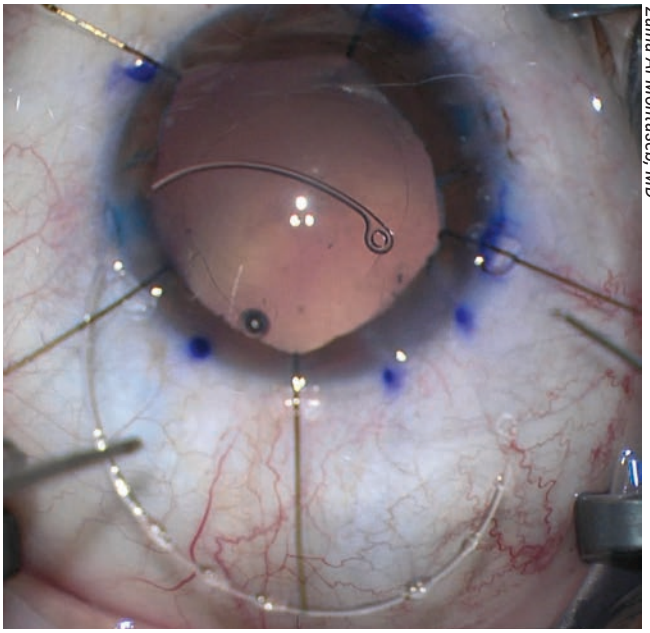
"Some surgeons might end up putting a capsular tension ring in at the same time as the capsule hooks to support the equator," he says. "But I find the capsule hooks are, in general, all you need.

"Once you have the lens out, you need to decide if you want to get by with just a capsular tension ring or add a scleral fixation device, such as an Ahmed segment or a Cionni ring segment," he adds. It depends on how many clock hours of zonular weakness are involved and whether it's progressive. Some of these pseudoexfoliation cases tend to progress and the patient can end up with a subluxed IOL seven or eight years after surgery. I put a capsular tension ring in all of these patients to respond to this possible situation in the future."

If your patient has extensive zonular loss and still has a lot of the cataract in place, Nick Mamalis, MD, a professor of ophthalmology at the John A. Moran Eye Center, University of Utah, urges you to support the capsular bag while you're removing what's left of the cataract. When removing the cortex, he recommends you do so more tangentially, instead of toward the center of the capsule, to minimize stress on the zonules.

"Spread out the forceps on the zonules, so you won't exacerbate the zonular tear," he adds. Once he gets his bag adequately fixated in one of these cases, Dr. Mamalis prefers to use a one-piece hydrophobic acrylic IOL with haptics. "It's easy to insert in the bag and holds up well if the bag is adequately supported," he notes.

Zonular dehiscence in these patients is probably more common than most ophthalmologists realize, according to Robert M. Kershner, MD, MS, FACS, chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College, Palm Beach Gardens, Florida. "More often than not, zonular dehiscence may not be obvious to the surgeon," he says.



Zaina Al-Mohtaseb, MD

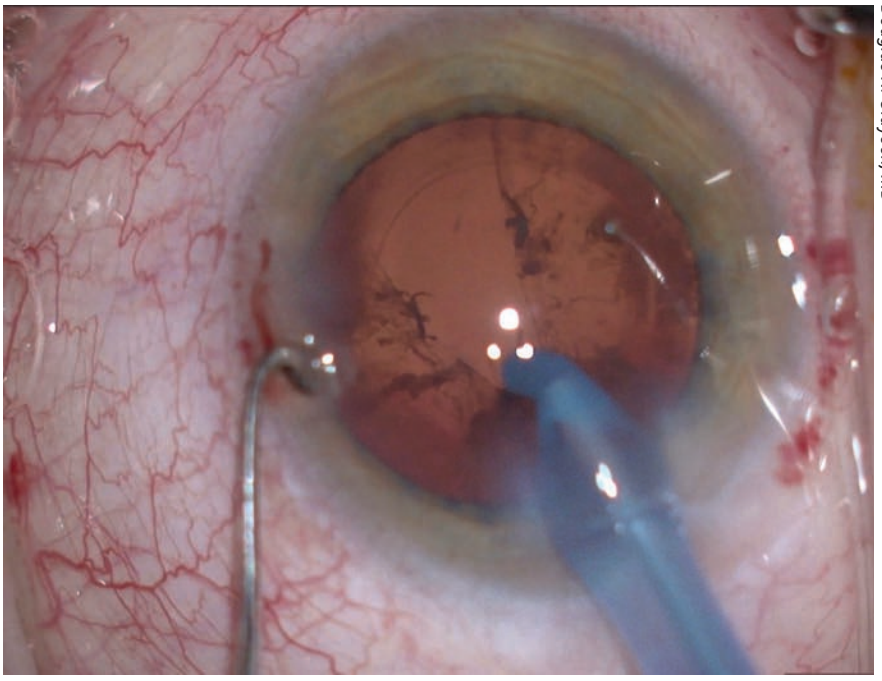
Figure 2. Weak zonules and poor dilation can be risk factors for posterior capsular tears. Using iris hooks and a capsular tension ring can decrease those risks.

If you're very conscientious and conservative about your surgery, staying within the center of the anterior chamber, Dr. Kershner says you might not notice or appreciate the effects of unsupportive zonules until you're fairly far along in your case. "It may become obvious only after you've removed the cataract or when you're about to implant the IOL," he says. "At one of those points, you may notice that part of the capsule is more toward the center than another part and that, possibly, even vitreous is starting to come around. So it pays to check for good zonular support when you start the procedure."

A Sudden Flat Chamber And Firm Eye

"The issue with a sudden flat chamber and firm eye is determining if you have a suprachoroidal hemorrhage or a choroidal effusion on your hands," says Dr. Kontos. "In such a case, I'm considering risk factors, such as a small eye or uncontrolled hypertension. There are only a few ocular emergencies in cataract surgery, and this is one of them. Sometimes, though, it's from balanced salt solution that's gotten through the zonules, putting pressure on the vitreous.

"If you confirm a suprachoroidal hemorrhage after evaluating the retina, then you immediately have to get the eye closed. Any instruments in the eye have to come out. If you have the ability to get a little bit of viscoelastic in there and then close up the eye with a suture, then do it."



Douglas K. Grayson, MD

Figure 3. Even after a posterior capsular tear, you may still have the opportunity to remove cortical material.

Dr. Hoffman says the most common cause of a sudden flat chamber and firm eye in his practice is the misdirection of infused fluid from the phaco tip. "Be that as it may, however, you still need to treat this as a potential choroidal hemorrhage, which could evolve into an expulsive choroidal hemorrhage, even though that's rare. So I will pull out of the eye and suture with one or two sutures to stabilize it."

Like many of his colleagues in this situation, Dr. Hoffman pushes his microscope aside and turns to a retinal specialist's indirect ophthalmoscope and 20-D lens, typically found in operating rooms, to study the retina for the dark brown color of a hemorrhage, the slightly different appearance of an effusion or an elevated retina. All of these signs signal a need to end surgery and refer the patient to a retinal specialist, he says.

"If, as usual, it's infusion misdirection, you can usually wait it out because that condition can improve on its own," Dr. Hoffman says. "You can go into your other OR to do another procedure or, if necessary, have the patient rolled to a waiting area for 30 to 60 minutes, while mannitol is administered. That eye will usually have softened up, allowing you to eventually finish the case, even if it has to be on another day in the unlikely event that it doesn't resolve during that brief waiting period."

In today's era of small-incision surgery, Dr. Mamalis gratefully acknowledges that the risk of an expulsive choroidal hemorrhage has been reduced. "Nonetheless, you want to get your anterior segment under control and even put in a suture immediately, if necessary," he says. If he sees evidence of a choroidal hemorrhage or effusion, he says he'll obtain an immediate consultation from a retinal specialist, who may wait 10 to 14 days for the clot to liquify and dissolve before working on the eye. "Once the retinal specialist has finished with the patient, you can go in and do what you need to do, whether it's removing some remaining material in the eye or putting in your intraocular lens in a more controlled setting," says Dr. Mamalis.

Broken Capsule with Lost Nucleus

Either all or a large part of the nucleus may be lost in these cases, surgeons note.

"This is one of those events that makes your heart go up into your throat," says Dr. Kontos. "You have to just stop the surgery and you have to fight the urge to go fishing for nuclear fragments. If you have a torn capsule and you've lost a piece of nucleus down in the vitreous, you have to accept that and realize this isn't the end of the world. You'll need to refer the patient to a retinal specialist. That's sometimes just part of cataract surgery."

Dr. Kontos removes what vitreous he can, hoping to avoid vitreous prolapse. "If there are any pieces of the nucleus that you can keep in the anterior chamber, use viscoelastic to elevate them and get them when you can before turning the case over to the specialist," he says.

When a capsule breaks on him, Dr. Hoffman determines if the anterior capsulotomy is still intact. "It usually is intact," he says. "I'll clean everything up, make sure there's no vitreous in the anterior chamber and try to get as much of the nucleus out as possible, with a combination of vitrectomy and phacoemulsification. If the whole lens or part of the lens has dropped, I clean up as much of the residual cortex as I can with my vitrectomy instrument, so that I'm not putting any traction on the vitreous. If the anterior segment is clean, I go ahead and put a three-piece lens in the sulcus and use optic capture to implant the optic through the intact capsulorhexis. You need to keep the vitreous from coming forward. Then you'll need to have the retinal specialist come in and clean up the mess that you've created in the back of the eye."

When one of his residents breaks a capsule, Dr. Mamalis is on alert. "I find that residents will often panic, and the first thing they want to do

is yank that phaco tip out of the eye," Dr. Mamalis says. "If they do that, the chamber shallows and the capsule will tear even more. You need to keep your foot on the pedal and go to position one. Then inject OVD through a stab incision, putting it over the capsule tear and inside your chamber."

Dr. Mamalis notes that you can still anteriorly remove fragments of nucleus without doing further damage. "You can even put a little lens glide underneath the fragments or you can put a wall of OVD underneath them. Then you can carefully remove what's left of that nucleus without having it sink back toward the retina. But don't be tempted to go in and get nucleus that's sunk posteriorly into the vitreous. That's a serious, costly error."

"When they perform a capsulorhexis, I tell surgeons to read the capsule," says Dr. Kershner. "If the capsule tears really easily and seems to be very thin, remember that the posterior capsule is going to be a third thinner than that." In such a patient, he continues, the risks of a broken capsule are extremely high.

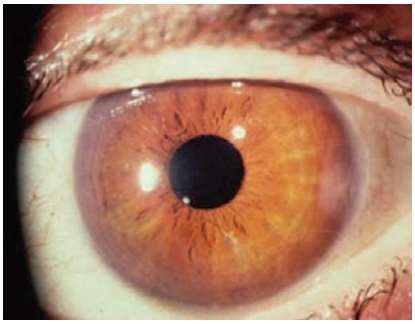
"The first thing to do is stop and recognize the adverse event as it occurs," he says. "If you have an anterior tear, your job is to make sure it doesn't extend posteriorly. And if it does extend posteriorly, make darn sure that you don't allow vitreous to escape through it. Worse yet, you could have the lens exit through the posterior capsular tear."

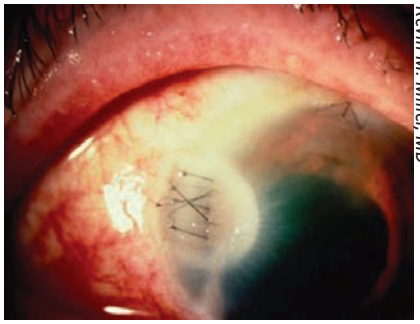
In very elderly patients, he notes, the risk of this type of complication is greatest because vitreous syneresis reduces or eliminates support behind the capsule. "Any tear is going to easily allow posterior vitreous contents in the vitreous cavity to enter the capsular bag and, possibly, the anterior chamber," he says. "In almost all cases, the better part of valor is to admit the complication, do the best you can to clean things up and close the wound securely so that the vitroretinal surgeon can step in to help."

Wound Burn

Although rare these days, a wound burn can still occur—suddenly and without warning. What are the best ways to avoid it and respond if it occurs?

"You just have to recognize it and stop phacoemulsification as quickly as possible," Dr. Kontos says. "Usually, it's because the phaco tip has become occluded and the fluid isn't able to flow through the needle. The heat builds up very quickly. You can see evidence of this if you keep a close watch on the tip of your phaco handpiece. You get this thick, milky-white material forming at the tip. That's your cue to stop your phaco and let the fluid continue to flow to provide irrigation. Usually, a wound burn occurs if you don't recognize it and you keep the phaco going."





Kevin M. Miller, MD

Figures 4 and 5. A wound burn, occurring in a flash, can go from minor (left) to severe (right) in a matter of seconds.

Once a burn occurs, how you should respond depends on the degree of the burn, according to Dr. Kontos. "You may have to go to a different site on the cornea to create a new wound," he says. "It depends on where you are in the case. Then the question becomes: How do you close the wound that was burned? You have to put in so many sutures and tie them so tightly that you will create a tremendous amount of astigmatism. What I was taught to do and have used successfully a couple of times is make a frown-shaped, relaxing incision posterior to the wound in the sclera. That lets tissue slide forward and allows you to suture the actual incision closed without creating as much astigmatism and needing to tie it quite so tightly. Then, you can usually use the new incision to complete the case, unless there's a reason not to continue right away, such as a burned wound that's leaking."

Dr. Hoffman says a wound burn is always possible if you're working on a very dense lens. "To avoid this, use energy that's modulated, so that your phaco isn't turned on continuously," he says. "For a patient with a very dense cataract, you might want to make your entry wound a little bit larger. This can result in a lot of fluid coming out around the eye and the phaco tip, which helps to keep the tip from getting too hot."

Another risk to avoid is working in a really tight wound, he adds. "In that situation, you're pulling up on the phaco needle and cutting off the infusion fluid," he says. "You could end up kinking the sleeve. Besides making sure you don't kink off the infusion and make the wound too small, use refrigerated balance salt solution and avoid oar-locking. If you take these precautions, your risk of causing a wound burn will be significantly reduced. If the patient has a rock-hard cataract, ask your assistant to focus on the phaco needle when it enters the eye and to let you know immediately if he or she notices anything unusual, such as the wound area getting white."

Once a burn has occurred, Dr. Hoffman says you can suture the wound closed if you've caught it early enough. "Sometimes you have to put in several cross sutures, but rarely do you have to glue it," he says. "Seal the wound as best you can and then move to make a new wound in a different location, probably a scleral incision 90 degrees away."

Although he's never had a wound burn occur in his hands, Dr. Mamalis says he has seen more than he'd care to when operating with his residents, some of whom charge into procedures too eagerly at times, risking this complication. To prevent this from occurring under his watch, he tells them to always enter the eye with just the irrigation turned on initially. "Then I tell them to aspirate some of that super-cohesive OVD," he says. "The idea is that you want to establish circulation of BSS around that phaco tip before beginning phacoemulsification."

Like Dr. Hoffman, Dr. Mamalis views a small, tight wound as a needless risk factor for a wound burn. "Avoid thinking you have to make your incision smaller than the last surgeon," he says. "Surgeons have a tendency to do that. If you make an incision that's too small and you have a phaco tip that doesn't properly fit the size of that incision, you can actually block off the circulation. Remember that you need to keep that needle cool. If you block off that flow, the heat that comes from the ultrasound can go up to 50 degrees centigrade in literally a second or two. That wound will turn white. You want to recognize it and respond before any other damage occurs. You need to immediately stop phacoemulsification but keep irrigating like heck on the surface before you pull out. Once that wound burn happens, it happens. There's nothing you can do but stop it from getting worse."

Do No Harm

Dr. Kershner, who's consulted with defendants and claimants on many eye surgery lawsuits through the years, says that any number of circumstances can arise that will challenge today's surgeon.

"Above all, though, one of the biggest problems I see is a failure to refer or get help," he notes. "Nobody will ever fault a surgeon for an unexpected adverse event, for a complication from surgery, unless that surgeon made it worse or denied it. So if you think about leaving it alone, that you're not going to do anything about it, this is what will get you into trouble. The term for that is 'falling below the standard of care.' What we do isn't always perfect. But we must always do whatever we can to serve the best interests of the patient. Remember the Hippocratic oath: *Primum non nocere*." ◀

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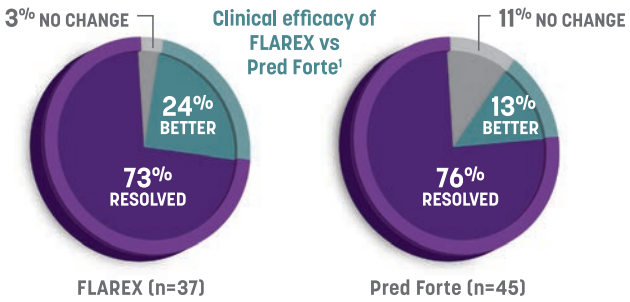
The power of Pred Forte* (prednisolone acetate ophthalmic suspension, USP) 1% with the safety of FML* (fluorometholone ophthalmic suspension, USP) 0.1%[1a]

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

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

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

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



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

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

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

INDICATIONS AND USAGE
FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.
IMPORTANT SAFETY INFORMATION
ADVERSE REACTIONS: Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.
Please see the Full Prescribing Information on the next page.

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

Flarex®
(fluorometholone acetate ophthalmic suspension) 0.1%

FLAREX NDC NUMBER: 71776-100-05

References: 1. Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol.* 1984;16(12):1110-1115. 2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification report. *Ocul Surf.* 2017 Jul;15(3):276-283. doi: 10.1016/j.jtos.2017.05.008. 3. FLAREX [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017. 4. US Department of Health and Human Services, Food and Drug Administration. *Approved drug products with therapeutic equivalence evaluations.* (Orange Book). 40th ed. Washington, DC: US Department of Health and Human Services, Food and Drug Administration; 2020. 5. National Center for Biotechnology Information, PubChem. Fluorometholone acetate. https://pubchem.ncbi.nlm.nih.gov/compound/ fluorometholone-acetate. Accessed September 10, 2020. 6. Sendrowski DP, Jaanus SD, Semes LP, et al. Anti-inflammatory drugs. In: Bartlett JD, Jaanus SD, eds. *Clinical Ocular Pharmacology.* 5th ed. St Louis, MO: Butterworth-Heinemann; 2008:221-244.

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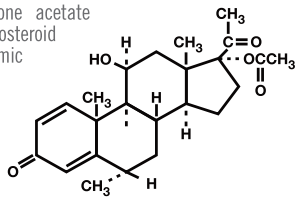
When it comes to ocular surface inflammation, FLAREX® is

A PROVEN WINNER

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



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

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

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

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

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

WARNINGS: FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION. Use in the treatment of herpes simplex infection requires great caution. Prolonged use may result in glaucoma, damage to the optic nerve, defect in visual acuity and visual field, cataract formation and/or may aid in the establishment of secondary ocular infections from pathogens due to suppression of host response. Acute purulent infections of the eye may be masked or exacerbated by presence of steroid medication. Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids. It is advisable that the intraocular pressure be checked frequently.

PRECAUTIONS:

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

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

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

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

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

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

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

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

Postmarketing Experience: The following reaction has been identified during post-marketing use of FLAREX® (fluorometholone acetate ophthalmic suspension) in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes: dysgeusia.

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

HOW SUPPLIED: FLAREX (fluorometholone acetate ophthalmic suspension) is supplied in white low density polyethylene (LDPE) bottles, with natural LDPE dispensing plugs and pink polypropylene closures. The product is supplied as 5mL in an 8 mL bottle.
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STORAGE: Store upright between 2°C -25°C (36°F -77°F). Protect from freezing.

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Optimizing Outcomes of Tube Shunt Surgery

Preoperative, surgical and postoperative pearls to help ensure the best possible outcomes with these patients.

STEVEN J. GEDDE, MD
MIAMI

Once we've decided that a patient would benefit from having a tube shunt implanted, we have to make a series of decisions. Those include which type of implant to use (valved or nonvalved), what size implant would be most appropriate, where to position the endplate on the eye, where to place the tube, how to deal with the delayed pressure control associated with using a nonvalved implant and what measures can be taken to minimize the risk of complications. Here, I'll share some strategies that can help you make the best decisions for your patient and ensure the best possible outcome.

Selecting an Implant

As you know, tube shunts fall into two categories: nonvalved implants and valved implants. The latter incorporate a flow-restrictor into the design that limits the flow of aqueous through the device if the pressure drops too low. The Ahmed implant (New World Medical) is currently the only valved implant that's in popular use. The Baerveldt (Johnson & Johnson Vision), Molteno (Molteno Ophthalmic) and the new Ahmed ClearPath (New World Medical) implants are all examples of nonvalved implants.

The first decision we need to make is whether a valved or nonvalved implant will best serve the patient we're managing. As always, it's best to base our decision on clinical trial data, in addition to our first-hand experience. Much of the information we have about the differences between these implants comes from two landmark clinical trials: the Ahmed-Baerveldt Comparison (ABC) Study and the Ahmed vs. Baerveldt (AVB) Study.

Clinical factors that would affect my choice of implant include:

• ***The patient needs a low postop pressure.*** The two major determinants of the final intraocular pressure after tube shunt surgery are the total surface area of the capsule around the endplate and the thickness of the capsule. There's not much we can do to modulate the thickness of the capsule; that's determined by the individual's healing process. But we can influence the surface area, because an endplate with a larger surface area will produce a larger-area capsule around the endplate, and thus a lower pressure. In fact, the clinical evidence supports this.

The Ahmed glaucoma valve's endplate has a smaller surface area than the Baerveldt and ClearPath devices, so using one of the latter two devices would make sense if you need to achieve a low pressure. For that reason, I tend to favor nonvalved implants like the 350 Baerveldt or the 350 ClearPath for patients who have advanced glaucoma or normal-tension glaucoma, where a low postop pressure is desirable.

• ***The patient has markedly elevated IOP.*** A valved implant makes sense for a patient in this situation because, unlike a nonvalved implant, you won't need to temporarily restrict flow through the implant at the time of surgical implantation. This offers the advantage of allowing immediate pressure reduction, while minimizing the risk that the IOP will drop too low.

• ***The patient has a high risk of hypotony.*** I favor a valved implant like the Ahmed in patients at higher risk of hypotony because the valve mechanism helps to prevent the IOP from going too low. That's particularly important in eyes that are prone to that complication, such as those with uveitic glaucoma; patients who have had prior cyclodestructive procedures; and also, in my opinion, patients who are significantly older—perhaps over the age of 85. The ciliary body makes less aqueous humor as we get older, so very elderly patients may be at a greater risk of hypotony.

• ***The patient is poorly adherent or intolerant of medication use.*** Larger-size endplates make sense for patients who are poorly adherent or have trouble tolerating drops. In both the ABC and AVB Studies, patients who received a Baerveldt implant required fewer glaucoma medications than those who received an Ahmed implant. Presumably this is related to the larger endplate providing greater efficacy.

• ***The patient has had a prior***

This article has no commercial sponsorship.

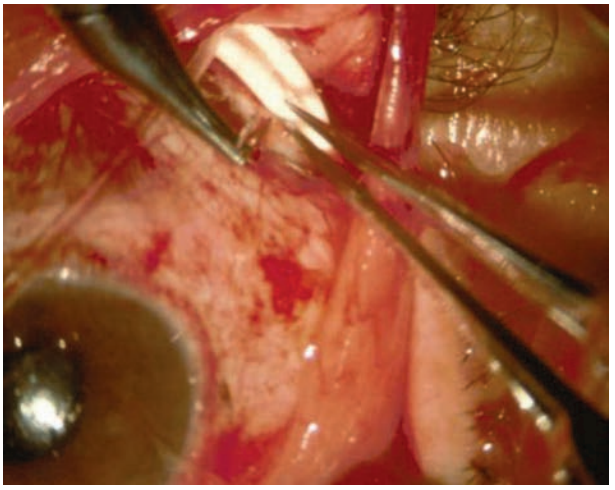
Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

scleral buckling procedure. Implanting a tube shunt in patients who have a scleral buckle around the eye can be tricky. I've found that an implant with a lower profile, like the nonvalved Baerveldt or the new ClearPath, can be easily positioned over the buckle. That may reduce the likelihood of migration and erosion of the device.

• ***Where you're placing the endplate.*** Most implants are placed in the superotemporal quadrant, but occasionally there's a reason to place it elsewhere. My preference for a fallback location is the inferonasal quadrant. (A more detailed discussion of inferonasal placement is provided later in this article.)

When inferonasal placement is indicated, I tend to favor a nonvalved implant, although you can put a valved implant inferonasally if necessary. A nonvalved implant like the Baerveldt has an endplate with anterior-posterior dimensions that make it less likely to encroach on the optic nerve, given that the optic nerve inserts nasally. That's of particular importance in eyes that are small, such as nanophthalmic eyes, and in children. It also has a lower profile and sits nicely in the inferonasal quadrant.

• ***The patient has neovascular glaucoma.*** I use a valved implant in these patients because of some interesting data from the ABC Study that was presented a few years ago at the annual meeting of the American Glaucoma Society. (This data hasn't been published yet.) In the ABC Study, a separate stratum was composed of patients with neovascular glaucoma; they were randomly assigned to either an Ahmed or Baerveldt implant. Remarkably, the data showed that neovascular glaucoma patients randomized to the Baerveldt group were about twice as likely to go blind as patients in the Ahmed group—a statistically significant difference.



Implantation of a Baerveldt glaucoma shunt and surgical placement of the tube.

What could explain a difference this large? I suspect it relates to ocular perfusion. Ocular perfusion is influenced by IOP and blood pressure—higher IOP and lower blood pressure are associated with lower ocular perfusion. Patients with neovascular glaucoma have impaired ocular perfusion, and this is the underlying cause of their disease. These patients typically have marked IOP elevation, and there appears to be a benefit of producing immediate pressure reduction with a valved implant, which results in improved ocular perfusion.

Beyond concerns such as these, choosing between the nonvalved implants is largely based on surgeons' preference. The new ClearPath implant has a lot of design features that are similar to the Baerveldt, especially with respect to surface area, and we don't have a lot of data that would suggest one is superior to the other. I'm mostly concerned with the surface area rather than the brand of implant, since the degree of pressure reduction seems to depend on that. (I have no financial interest in any of the implants.) If a nonvalved implant is my choice for a patient, I generally pick one that has a large-surface-area endplate, such as the 350 Baerveldt or 350 ClearPath, expecting that it will produce a greater IOP reduction.

Bridging the Gap

When implanting a nonvalved device like a Baerveldt or ClearPath, the surgeon must temporarily restrict flow through the device to avoid postoperative hypotony. The capsule surrounding the endplate provides the resistance to aqueous outflow, but that capsule takes several weeks to develop. I usually temporarily restrict flow through the tube by ligating it with a 7-0 vicryl suture. That suture will dissolve four to six weeks after surgery—adequate time to allow the capsule to form around the endplate.

However, this approach makes the tube shunt nonfunctional. There are several ways to provide IOP control in the early postoperative period until the tube opens:

• ***Restart medical therapy.*** One approach is to simply put the patient back on medical therapy. That probably wasn't adequate to provide long-term pressure reduction or you wouldn't be doing surgery, but it might be adequate as a temporizing measure until the tube opens up.

• ***Orphan trabeculectomy.*** Another option is doing an orphan trabeculectomy at the same time as your tube shunt surgery. Of course, you probably decided to implant a tube shunt because you felt a trabeculectomy would have a high probability of failure. However, an orphan trabeculectomy is one that you're only counting on to work for a few weeks, to keep the pressure low until the tube opens up and provides more long-term pressure reduction.

• ***Create venting slits in the tube in front of the tie-off point.*** This is referred to as tube fenestration. When I make fenestrations, I usually make several, using a TG 140 needle (the spatulated needle on the vicryl suture). This approach is actually quite effective at providing pressure reduction, although it's a

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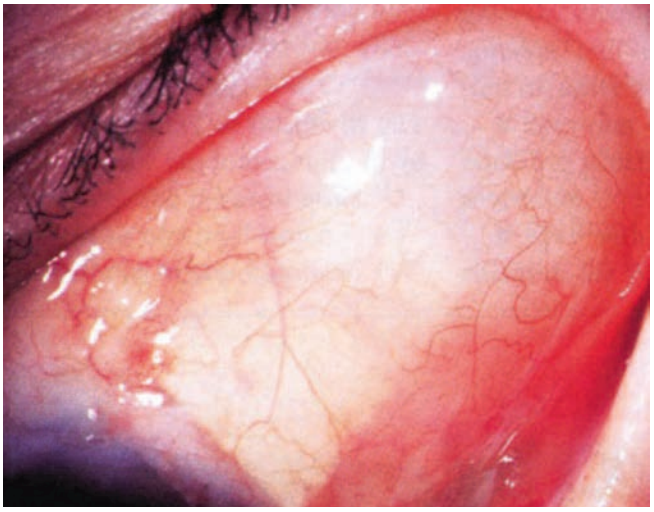
Reference: 1. Jones L, et al. TFOS DEWS II Management and Therapy Report. *The Ocular Surface.* 2017;15:575-628.

M2O-036-00A

little less predictable than a trabeculectomy or using a valved implant.

• ***Create one slit in the tube and leave a suture in it to act as a wick.*** I learned this technique from Jamie Brandt, MD. He makes a little slit in the tube, like a standard fenestration, but leaves a 9-0 monofilament vicryl micro suture in the tube to serve as a wick, promoting aqueous egress. He calls this the "vent and stent" technique. It's another option for early pressure reduction when using nonvalved implants.



A postoperative photo showing a bleb overlying the endplate of a Baerveldt glaucoma implant.

Inferonasal Placement

We usually put tube shunts in the superotemporal quadrant, because the surgical exposure is generally easiest in that area. However, there are some reasons to do otherwise, and in those situations, Paul Sidoti, MD, has pointed out the value of inferonasal placement.

Reasons for avoiding superotemporal placement of a tube shunt include:

— There's already an implant in the superotemporal quadrant, and a single tube shunt isn't sufficient to control the pressure.

— There's a lot of scarring of the conjunctiva superiorly.

— There's a very large filtering bleb above that you'd like to avoid.

— The eye has thinning of the sclera. Patients with rheumatoid arthritis or a history of scleritis may have progressive thinning of the sclera.

— The cornea may be scarred superiorly, making it difficult to see the tube.

— There are a lot of peripheral anterior synechiae superiorly and you're planning anterior chamber tube placement.

— The eye has silicone oil in it (sometimes used when treating complex retinal detachments). In this situation we generally don't like to put a tube superiorly, because if any silicone oil migrates into the anterior chamber—which occasionally happens—it will find its way into the tube and drain into the subconjunctival space. In contrast, oil isn't going to go towards an inferior location because it floats.

As it happens, putting an implant into the inferonasal quadrant is easy. In many ways it's just as easy as putting it in the superotemporal quadrant. So, I have a pretty low threshold for putting an implant in the inferonasal quadrant. (You also can put valved tube shunts like the Ahmed in this quadrant.)

A few other tips when placing a tube in the inferonasal quadrant:

• ***Be careful in patients with small eyes, such as infants or patients with nanopthalmos.*** A small eye can be problematic because the optic nerve inserts into the back of the eye a bit nasally, making it possible that the endplate could press on the optic nerve. (Sharon Freedman, MD, at Duke University has a wealth of experience treating pediatric glaucoma; she's developed an online calculator that will tell you how far back you can place the endplate to avoid encroaching on the optic nerve, as long as you know the patient's axial length. It's available to anyone at people.duke.edu/~freed003/GDDCalculator/. It's a great resource in these unusual circumstances.)

• ***Route the tube to the 6 o'clock position.*** There's less coverage of the scleral surface by the lower lid compared to the upper lid. Having inferior tubes routed to the 6 o'clock position maximizes the amount of tube that's covered and protected by the eyelid.

• ***Use a corneal patch graft.*** With inferior tube placement, there's less coverage by the eyelid, so I always use a transparent corneal graft. (These grafts are readily available.) You can use this for a superior placement as well, but in that situation it's OK to use sclera, or other nontransparent materials, because the patch graft is usually fully covered by the upper lid.

Other Pearls

These strategies will also help ensure a good outcome:

• ***When creating a track for the tube, make sure you're entering the anterior chamber parallel to the iris plane, and lift the needle a little bit as you enter the chamber.*** In my experience, creating a track for tube entry is the only part of the implantation procedure that requires a bit of finesse. One of the major complications from tube shunts is corneal decompensation. That's largely related to the position of the tube—in particular, if it's too close to the cornea.

The technique of lifting the needle upward towards the microscope a little bit as you're entering the anterior chamber helps prevent the tube from ending up more anterior than you had planned.

• ***Make a longer tube track through the sclera.*** It's important to minimize the risk of tube erosion after the surgery. Making a longer track by tunneling several millime-

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ters in the sclera before ultimately entering the anterior chamber serves to minimize the risk of the tube eroding through the sclera and conjunctiva, which would increase the risk for endophthalmitis. (An erosion usually requires a trip back to the OR to resolve it.)

To further reduce the risk of tube erosion I also put a patch graft over the limbal portion of the tube. I think of this as a "belt-and-suspenders" approach to help prevent any chance of erosion.

• ***If you're not happy with the position of the tube in the anterior chamber, take it out and make another entry incision right next to the first one, until you're happy with the tube position.*** The tube is frequently not perfectly positioned on the first try. When that happens, I just make another entry incision. If I'm not happy with the tube position intraoperatively, it's unlikely that I'll be happy with it postoperatively. So, take your time and make sure you get it right while you're in the OR.

• ***If you're implanting into a child's eye, leave a little extra tube length on the outside of the eye.*** This is another tip from Dr. Freedman. Route the tube in an "S" configuration on the scleral surface rather than making a direct entry path into the eye. Children's eyes are still growing, so the tube could eventually retract from the eye if there isn't adequate length.

• ***If a scleral buckle is present, position the implant based on the position of the buckle.*** If the buckle is very anterior in location, you can slip the implant behind it. But if the buckle is more posteriorly placed, you can position the endplate on top of the buckle. In this situation, I prefer to use a Baerveldt or ClearPath, because they both have a very low profile, which makes sense when your placing one implant on top of another.

• ***When placing an Ahmed implant, fill the anterior chamber with Healon at the end of the procedure.*** We want to avoid large drops in IOP in glaucoma patients, because that's a known risk factor for suprachoroidal hemorrhage. However, in patients with very high preoperative pressure I often use valved implants like the Ahmed, where the tube is open from the beginning. This Healon strategy, which I learned from Kuldev Singh, MD, allows for a more gradual reduction of pressure as the viscoelastic slowly drains during the first couple of days following the procedure. I haven't had any problems with postop pressure spikes using this approach. ◂

ABOUT THE AUTHOR

Dr. Gedde is a professor of ophthalmology and vice chair of education at the Bascom Palmer Eye Institute in Miami. He has no personal financial ties to any product mentioned.

Thinking of Trying MIGS?

(Continued from p. 43)

develop both a skill set that allows successful surgery and an understanding of how to manage intraoperative and postoperative complications."

• ***Check the pigmentation in the angle before surgery.*** Dr. Sheybani points out that one of the few ways you can get into trouble with MIGS angle procedures is if you're working at the ciliary body band and you're counting on pigmentation to guide you. "In some angles, the pigmentation is very light," he points out. "If that's the case, it's possible to misidentify the angle structures and create a cleft; that could lead to a lot of bleeding and possibly hypotony. It's rare for that to happen, but that's the big danger.

"This is one reason you need to examine the angle before surgery," he says. "If the pigmentation is really light, Trypan blue can be used to stain the trabecular meshwork nicely and give you clear landmarks to guide you. If you're considering doing a MIGS procedure and the pigmentation is very light, write a note in the chart to remind yourself to use Trypan."

• ***Avoid MIGS if inflammation is present.*** "If the eye is calm and quiet with a history of uveitis, sometimes MIGS works well," notes Dr. Grover. "But if there's active inflammation or neovascular glaucoma, I'd categorically avoid MIGS."

What can I do to help ensure better outcomes?

These strategies can help ensure optimal MIGS results:

• ***Avoid pushing down with the gonioprism.*** Dr. Sheybani says this is mostly an issue with surgeons who've done very little gonioscopy—especially residents and fellows. "When you're holding the gonioprism in your hand, there's a tendency to want to push down," he explains. "That can cause a lot of striae. The gonioprism should be coming on and off the cornea; if it has a light-touch meniscus that comes and goes, then you know you're doing it right."

• ***Don't push into the angle too hard during goniotomy.*** "Many surgeons do this," says Dr. Sheybani. "Pushing too hard can create striae, and you can hit the back wall. You need to use a light touch. You should think of it as kind of working back toward yourself. I had a fellow who said, 'It's almost like you're scooping things out of the canal.' That's a nice way to describe it. You really shouldn't be pushing in."

• ***Early in the surgery, don't have the patient look left or right while you're hovering in the angle with your device.*** "If the patient looks the wrong way, you could hit tissue and cause a problem," Dr. Sheybani explains.

• ***During surgery, make sure the patient's head is turned far enough away from you.*** "Surgeons sometimes complain they couldn't get a good view of the angle," says Dr. Sheybani. "The number one reason is that they didn't turn the head far enough away from them." ◂

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Back to Basics: Using OVDs

Know how to optimize your surgical results and stay out of trouble.

SEAN MCKINNEY
SENIOR EDITOR

Despite the appearance of increasing numbers of branded OVDs, many surgeons take the use of viscoelastics, or ophthalmic viscosurgical devices, for granted when performing cataract surgery. Although the core functions of OVDs haven't really changed, experts nonetheless point to a continuing need to better understand and embrace their complex behavior for optimal use.

Steve Arshinoff, MD, FRCSC, an associate professor in the Department of Ophthalmology and Vision Sciences, University of Toronto, and a clinical assistant professor at McMaster University in Hamilton, Ontario, Canada, says the best way to meet this need is to focus on the two basic properties of OVDs: viscosity and cohesive-dispersive behavior. "There are no OVDs that are both cohesive and dispersive; they all fit somewhere along a line from very cohesive to very dispersive" says Dr. Arshinoff, a pioneer of many OVD techniques.

In this report, Dr. Arshinoff joins other leading surgeons to help you better understand where your OVDs are along that line and at what degree of viscosity the next time you reach for one to undertake a specific surgical task.

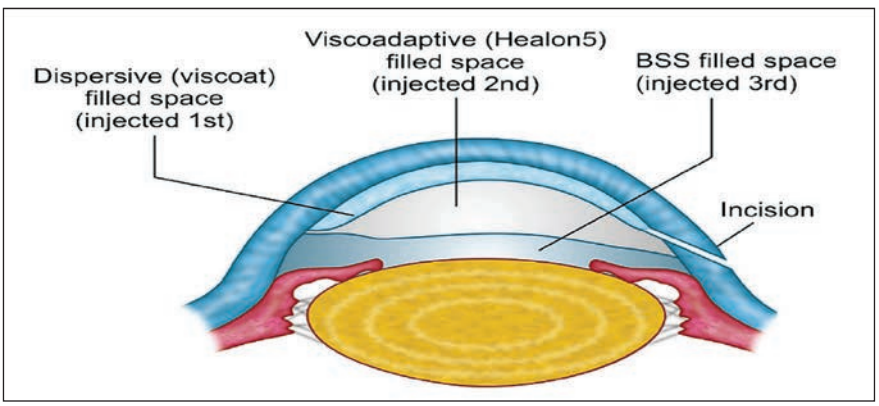
Basic Functions

For basic cataract surgeries, OVDs are used to maintain space and protect tissues. "Protecting tissues also means compartmentalizing, keeping some parts of the inside of the eye in one place and other parts in a separate place during certain parts of surgery," says Kevin M. Miller, MD, Kolokotrones Chair in Ophthalmology, University of California, Los Angeles. "At the start of surgery, you're powering through the cataract using ultrasound. You want to protect the cornea and iris from the ultrasound and the flying fragments. Coating these tissues is the most important function of an OVD at that stage."

Once the cataract has been removed, he continues, "space maintenance becomes a high priority. When you're going in and out of the eye with instruments, the infusion line doesn't provide enough support. The chamber is now at risk of collapsing. Cohesive OVDs help prevent a collapse by maintaining space. OVDs are also good for opening things up—such as the capsular bag."

The physical properties and characteristics of OVDs are determined primarily by the molecular chain length and concentration of their principal rheologic components, according to D. Michael Colvard, MD, who is clinical professor of ophthalmology on the volunteer faculty at Jules Stein Eye Institute, David Geffen School of Medicine UCLA, and director of the Colvard-Kandavel Eye Center in Encino, California. "These properties and characteristics also change in a predictable fashion under different conditions of fluid movement (turbulence) within the eye," he adds.

The viscous-cohesive OVDs such as Healon GV and Healon (Johnson & Johnson Vision) and Provisc (Alcon) are long-chained sodium



Steve Arshinoff, MD, FRCSC

Figure 1. The layering of dispersive and visco-adaptive OVDs on top of BSS, referred to as the Tri-Soft Shell Technique (TSST), is one of several "soft shell" techniques that provide specific benefits, this one to protect the inner cornea against endothelial loss.

This article has no commercial sponsorship.

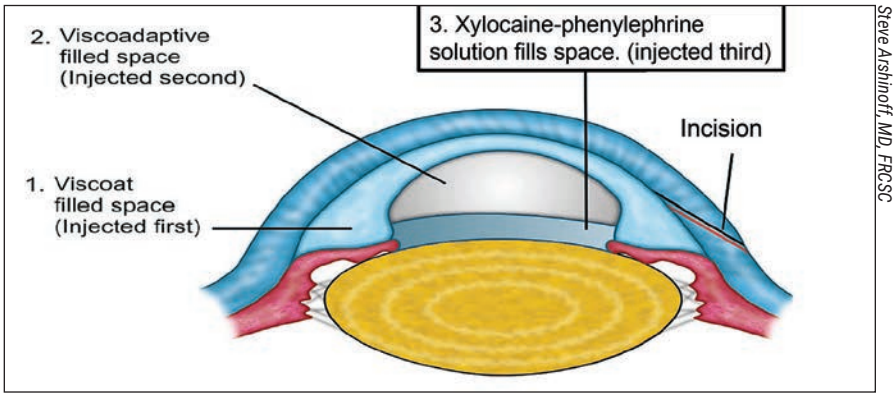
Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.

hyaluronate OVDs with a molecular weight of 2 to 5 million Daltons, Dr. Colvard notes. They're referred to as "cohesive" because they cohere since their long molecular chains tend to intertwine, causing them to behave intraocularly as a cohesive unit. The advantages of cohesive OVDs are that they maintain space well, stabilize structures and enable pressurization of the space they occupy.

"A cohesive OVD will help you maintain a deep anterior chamber and prevent the incision from leaking, unless irrigation raises the intraocular pressure too high, in which case it will burp out as one piece," adds Dr. Colvard. "In addition, cohesive OVDs are also easier to aspirate at the end of surgery, but this benefit also has a downside: In the presence of irrigation and aspiration, it means the materials won't necessarily remain in the eye to provide a high level of endothelial protection during prolonged phacoemulsification."

Dr. Colvard says dispersive OVDs such as Viscoat (Alcon), Endocoat (Johnson & Johnson Vision) and the new ClearVisc (Bausch + Lomb) are low-molecular weight, short-chained sodium hyaluronate OVDs (approximately 500,000 to 800,000 Daltons). Viscoat also contains low molecular weight chondroitin sulfate, which Alcon claims enhances endothelial protection. ClearVisc includes sorbitol, which Bausch + Lomb says protects the cornea against free radicals spawned by phacoemulsification.

"OVDS with low molecular weights are considered dispersives because their short molecular chains don't become entangled as easily, allowing the OVD mass to come apart more easily," says Dr. Colvard. "The advantage of these OVDs is that during times of high-fluid turbulence, they resist being completely washed out better than cohesive OVDs do. The downside of dispersive OVDs is that they don't maintain space or enable pressurization as effectively as cohesive OVDs, and they're more difficult to remove from the eye at the completion of surgery."



Steve Arshinoff, MD, FRCSC

Figure 2. OVDs can be used to manage intraoperative floppy iris syndrome by employing the IFIS Soft Shell Technique (IFIS SSB), as shown above.

When considering OVD properties, recognize the unique nature of "visco-adaptives." They include Healon5 Pro (Johnson & Johnson Vision), composed of a higher concentration of sodium hyaluronate (2.3 percent) with a molecular weight of 3,200,000 Daltons, as well as other visco-adaptives not sold in the United States. Among those in the United States are Healon GV Pro, a super viscous-cohesive with a concentration of 1.8% sodium hyaluronate, and Healon Pro, a slightly lighter agent with a concentration of 1% hyaluronate.

Each contains the same length of hyaluronate chains, in different concentrations. The concentration in Healon5 is so high that it transforms an ultra-viscous cohesive at low flow rates to a fracturable solid when exposed to flow rates exceeding 25 cc per minute, according to Drs. Covard and Arshinoff. "Because of visco-adaptives' higher sodium hyaluronate concentrations, and their behavior as fracturable solids under high flow, allowing them to become trapped behind IOLs, we need to remove visco-adaptives thoroughly to prevent postop IOP spikes," Dr. Arshinoff says. The Ultimate Soft Shell Technique, an approach designed for visco-adaptives that's explained below, is ideal for this use, he says.[1]

Two for All

Dr. Arshinoff emphasizes the importance of using cohesives and dispersives together effectively.

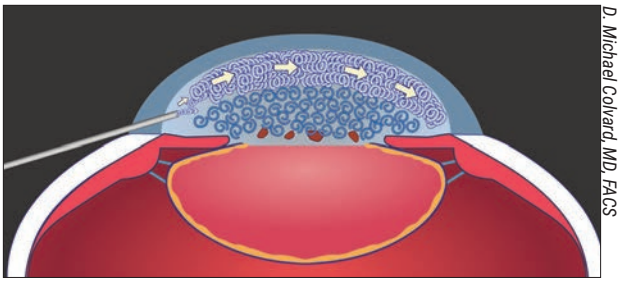
The most common combined use occurs when using the Soft Shell Technique, introduced by Dr. Arshinoff in the 1990s.[2] "A small amount of dispersive OVD is placed on the lenticular surface and then behind that a larger amount of cohesive OVD," he says. "The cohesive pushes the dispersive up against the cornea into a smooth layer, which has many advantages. First, the dispersive remains longer because its smooth edge doesn't get caught by the balanced salt solution turbulence, preventing it from washing off easily. Furthermore, using a dispersive this way minimizes its irregular surface boundaries, which can cause blurring when it's flowing. With the dispersive pressed against the cornea, you see better through a smoother layer of OVD, making surgery easier."

The SST can help during just about all types of phaco cases, Dr. Arshinoff continues, and it's best to use it with OVDs whose properties are as different as possible. "There is less endothelial cell loss," he notes. "And you can pressurize the eye better if you use a dispersive with a cohesive in a structured method."

Endothelial Dystrophies

Although the SST, in use for more than 20 years, is the most commonly used OVD technique in the world, Dr. Arshinoff says that it's "not well understood" by all surgeons. "Some

surgeons even say they can do cataract surgery without using any OVDs," he notes. "Well, you can, but you will get more endothelial cell loss. This is particularly critical in patients with Fuchs' endothelial dystrophy or other causes of decreased endothelial cell counts. When you see these patients in seven or more years, you'll find they've lost more of their corneas, due to endothelial decompensation, than they would have after SST or other soft-shell techniques."



D. Michael Colvard, MD, FACS

Figure 3. By directing the flow of cohesive OVD anteriorly after phacoemulsification, you can visco-dissect any dispersive OVD left in the anterior chamber away from the endothelium and toward the pupillary plane.

To ensure the best long-term outcome in these cases, he also recommends lowering the flow to about 15 cc per minute. "At low-flow rates, you don't lose the Healon5 behind the Viscoat, because Healon5, being a visco-adaptive, will act like an ultra-viscous cohesive OVD and resist aspiration at low flow rates. You'll be operating in a very small space behind the Healon5 in the capsular bag, and nothing in the anterior chamber will move. When you finish the case, you can take out the Healon5 layer, but you can leave behind the very thin layer of the dispersive Viscoat. The postop IOP spike that may occur from leaving a small amount of OVD can be reduced with topical drops. It's less of a concern than the cell loss you would have caused by trying to wash it off."

Dr. Miller also uses OVDs to protect a compromised cornea, relying on dispersives. "We need to keep in mind that endothelial cells never regenerate, and we continue to lose them as we get older," he observes. "This process accelerates as a result of trauma, surgery or inflammation inside the eye."

During a typical cataract procedure, he continues, a patient loses 3 to 8 percent of his or her endothelial cells. "If a patient starts with a low number of cells and loses another 3, 4, 5 or even 10 percent, that can lead to swelling of the cornea, a blistering cornea or bullous keratopathy, from which the patient never recovers. That would require a corneal transplant of some sort."

Other Uses of OVDs

Dr. Miller notes that dispersive OVDs can also help by compartmentalizing vitreous to keep it from following the phaco tip out of a surgical wound. "You can also compartmentalize lens fragments with dispersives," he adds.

In addition, he says, a cohesive OVD can be used to expand a pupil. "This is accomplished through viscomydriasis," he says. "For a patient who doesn't dilate well, despite the administration of drops, you can put in a Malyugin Ring or pupil hooks, of course. But Healon5 can also be used to really open the pupil widely."

After a capsulorhexis, while using hydrodissection, you may sometimes find you're not able to free up a patient's epinucleus and cortex. "Taking the path of least resistance, the fluid coming out of your cannula does a U-turn and comes right back at you," says Dr. Miller. "Here, a cohesive or even a dispersive OVD can help by visco-dissecting all of the stuff that's stuck."

He notes that an OVD can also help when a capsule breaks, causing a release of vitreous. "You can put some OVD over the capsule break or in an area of a zonular compromise, compartmentalizing these structures. In the event of a capsule break, when pieces of nucleus or epinucleus start to fall, often you can get beneath those pieces with viscoelastic, performing what we call viscoelevation. You can start to fill up the vitreous cavity with the OVD and, as those pieces rise on the OVD, retrieve them before they drop onto the retina."

Dr. Arshinoff lists other special considerations when using OVDs, such as operating on a high hyperope with a very shallow chamber. "The main thing you want to achieve for this patient is to deepen the chamber," he says. "Using Healon5, especially with a very thin layer of balanced salt or xylocaine-phenylephrine (or adrenaline) solution behind it, adjacent to the anterior capsule (using the USST), enables you to make the rhexis much more easily." In addition, in cases involving a compromised cornea, the Tri-Soft Shell Technique, which is a combination of the SST and USST, adds more advantages, he notes.[3]

Another case might involve a -20-D myope with an excessively deep chamber, making access to the nucleus difficult. "Inserting less Healon5 maintains a stable, but more shallow, anterior chamber," says Dr. Arshinoff. "The Healon5 maintains the chamber because it blocks the incision. But the lens moves forward a bit, which you can titrate by the amount of Healon5 you inject into the anterior chamber, making it easier to create the rhexis in a high myope, instead of having to stretch back deep into the eye."

FLACS and Other Challenges

Dr. Arshinoff says OVDs can also help prevent incomplete capsulotomies that can potentially tear out during femtosecond laser cataract surgery. Using a small cannula in front of the capsule, he says, slowly inject Healon or Healon GV until the flap moves posteriorly and becomes slightly concave.

"If the flap is attached to part of the peripheral capsule, alternate injecting the OVD through the main and sideport incisions," he says. "Because

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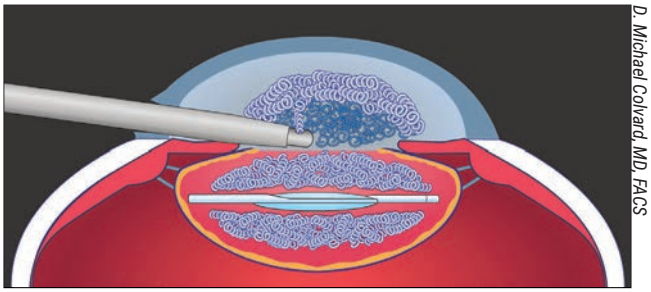
the incisions are usually 95 to 100 degrees apart, you can move the capsule back and forth with OVD injections to get it flat and slightly concave. Then use tiny forceps to pull the capsule posteriorly and toward the middle, which makes the capsule tear centrally and not peripherally, as you would risk doing by folding the flap over anteriorly to tear it."[4]



D. Michael Colvard, MD, FACS

Figure 4. This maneuver places the dispersive OVD in a position in the anterior chamber where it can be more readily aspirated. This helps guard against postop IOP spikes.

For the implantation of phakic lenses, such as the EVO Visian collamer-based ICL (Staar Surgical) and the Artisan Phakic IOL (Ophtec), Dr. Arshinoff says one of the biggest challenges is removing the OVD at the end of the case without damaging the crystalline lens because of turbulence from the I/A. In these cases, he recommends using an OVD that you can wash out with gentle irrigation from a syringe. One example would be a hydroxypropyl methylcellulose solution, such as OcuCoat (Bausch + Lomb).

"If you're using the Yamane surgical technique for a secondary IOL, consider using Healon or Healon GV," he says. When implanting a secondary phakic IOL, he says, "remember that you have a very simple purpose for which you're using the OVD: You want stability to transiently create space and protect adjacent structures. You need to get the lens in the eye, position it properly and come out of the eye carefully."

Similarly, to capture an IOL in the capsulorhexis, Dr. Arshinoff urges you to be careful with your OVD choice, recommending Healon or Healon-GV so that you can wash it out more gently with a syringe and without needing to use I/A. "You also don't want to use dispersives because they're harder to wash out," he adds.

Dr. Arshinoff says that most IFIS cases can be managed with an approach he calls the IFIS Soft Shell Bridge Technique, a variation of the Tri-Soft Shell Technique.[6] First, you'd cover the iris with Viscoat in the angle all around the patient's eye. Second, he says, you'd bridge the center of the anterior chamber with Healon5.

The third step is for you to stretch the pupil, which will not flop when covered and tamponaded with an OVD. Fourth, under the Healon5 layer, you'd inject a layer of xylocaine-phenylephrine solution to enhance pupil dilation. Finally, he explains that you'd perform phacoemulsification with a flow rate of 15 to 20 cc per minute, enabling the OVD to remain stationary throughout the procedure. "Taking this approach is simple and much easier than using rings," argues Dr. Arshinoff.

Applying the Pressure

The final concept Dr. Arsinoff emphasizes involves the three levels of pressure when using OVDs:

• ***High pressure.*** Many surgeons prefer to work in high-pressure environments, using phaco machines that raise IOP to 60 or 80 mm Hg. "Higher pressure can be achieved with Healon5, Healon GV or with the use of different OVDs during SST," he says.

• ***Medium pressure.*** Surgeons who use only dispersive OVDs primarily work in a medium-pressure environment. "Adaptations must be made to achieve some results in a lower-pressure environment," says Dr. Arshinoff. "For example, avoiding the Argentinean Flag sign in a hypermature cataract is much easier with visco-adaptives, which can pressurize the anterior chamber to make the center of the anterior capsule concave for capsulorhexis.[5] Reducing pressure makes this much more difficult."

• ***Low pressure.*** Relying on low pressure, the opposite of what you would do when using visco-adaptives, is a typical approach in developing countries, where the cost of devices is a barrier. "Surgeons in those countries have devised ingenious techniques to manage cases in more difficult, low-pressure surgical environments," Dr. Arshinoff says.

Why to Choose Wisely

What all of this means is that you can perform all of the steps that these experts have described by using randomly selected OVDs or no OVDs at all.

"But you'll end up doing so with difficulty and, frequently, suboptimal results, compared to using OVDs that are optimally designed for what you're trying to achieve," says Dr. Arshinoff. "Each step of surgery is much easier when using the appropriate OVD. No OVD is ideal for everything." ◀

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DISCLOSURES

Dr. Arshinoff has Dr. consulted with every major manufacturer of OVDs. **Dr. Miller** is a consultant for J&J Vision and Alcon. **Dr. Colvard** reports no relationships with companies that make products related to this content.

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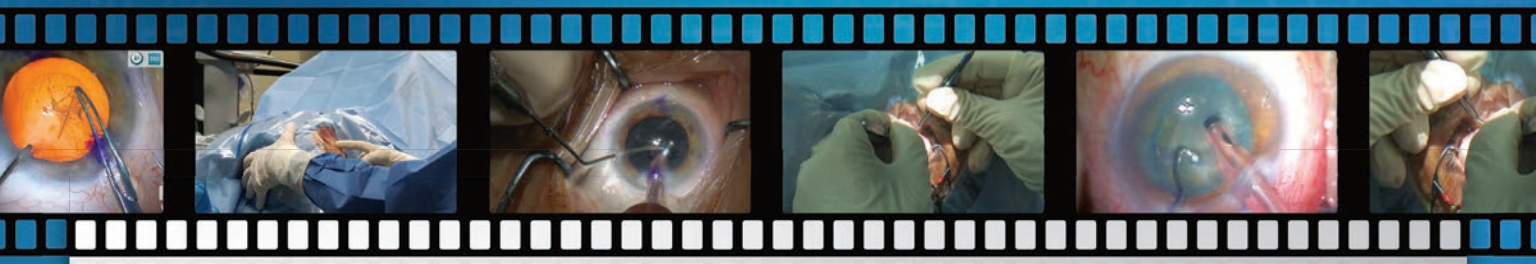

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Pediatric Ocular Trauma And the Pandemic

Kids being confined to quarters for a year or longer has affected the rates and kinds of trauma physicians are seeing.

ALICIA CASELLA AND
KARA M. CAVUOTO, MD
MIAMI

The COVID-19 pandemic has radically changed almost every aspect of our lives, including the rate and nature of pediatric ocular trauma. Though data from early in the pandemic implies a decrease in these cases, perhaps due to less time spent in motor vehicles and the cancellation of sports and recreational activities, physicians and parents must remain aware of shifting trends and possible new risks to children's eye health, since the visual pathways in these patients are still developing, and any trauma can have severe long-term effects. In this article, we'll provide a look at how the COVID-19 pandemic has changed the frequency of emergency department visits, created new hazards and altered the main causes of eye trauma in the pediatric population, as well as share tips on how to respond to particular types of ocular trauma often encountered during the pandemic.

The Pandemic Effect

Pediatric ocular trauma accounts for an estimated one-third of all eye-related emergency department visits in the United States each year, occurring at a rate of one injury every three minutes in a 2018 study.[1] When the COVID-19 pandemic was declared a national emergency on March 13, 2020, however, emergency medical care sought for reasons other than COVID-19 sharply declined.[2] A retrospective cohort study found that pediatric ocular trauma ED visits dropped by 51 percent from early to late March of 2020.[3] Public fear of contracting the virus in hospitals peaked during this time and, as lockdown restrictions were put into place, children began spending increasing amounts of time at home engaging in more sedentary activities with less risk of eye injury.

During the pandemic, different kinds of ocular trauma have become prominent.

In April 2020, the number of pediatric eye-related ED visits dropped even further, to 30 percent of the pre-COVID volume, bringing pediatric eye-related ED visits to the lowest figure seen in the study. It was during this time that the Kawasaki-like pediatric multi-systemic inflammatory condition was found to affect children, which may have further increased parents' worries over their children's safety.[3] Mandates keeping children from participating in sports/recreational activities and less time spent in motor vehicles, both of which typically comprise a large proportion of acute pediatric eye injuries, most likely also played a significant role in reducing the incidence of such trauma.[3]

However, the decrease in ocular trauma may seem counterintuitive considering that pediatric ocular trauma tends to occur in the home.[3,4] The decrease may be due to increased parental supervision, as parents and caregivers spent more time at home with their children during the pandemic due to the need to work remotely and/or fewer job-related responsibilities outside of the home. With social distancing efforts in place, children may also have been less likely to gather with friends and instead engaged in more sedentary, less-risky activities. It's also important to consider that ED visits for ocular trauma may have declined due to a lack of health insurance, as patients were 67 percent less likely to have health insurance after the start of the pandemic.[5] This lack of insurance may have resulted in fear of not being able to afford the cost of an ED visit and might have deterred parents and caregivers from seeking treatment.

Hand-sanitizer Injuries

While the decrease in eye trauma seen during the pandemic is a promising statistic, physicians and parents must remain aware of factors and exposures that may be more prevalent. One such exposure is the use of alcohol-based hand sanitizers, which

This article has no commercial sponsorship.

Dr. Collinge is an assistant professor in the Department of Pediatrics of the University of Connecticut School of Medicine. She has no financial interest in any of the products discussed in the article.

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REVIEW of OPHTHALMOLOGY

are being used frequently during the pandemic.

While the use of hand sanitizers is undoubtedly necessary to hinder the spread of the virus, such widespread use may also have negatively impacted children's eye health. A study conducted in France for the French Poison Control Centre Research Group showed a sevenfold increase in the number of alcohol-based hand sanitizer eye exposures in children and identified several cases of serious corneal lesions. One aspect that might be contributing to this issue is the fact that many sanitizer dispensers are placed in proximity to the level of younger children's faces. In addition, the composition of sanitizers is highly variable, and other additives may further promote ocular surface irritation and toxicity. Even alcohol-based hand sanitizers following World Health Organization recommendations contain 80% ethanol or 75% isopropanol, both of which can cause immediate cell death of corneal epithelial cells.[6] Practitioners and parents should be aware of the potential damage alcohol-based hand sanitizer can cause to children's eyes, to help prevent such occurrences.

If a child presents with a chemical burn from hand sanitizer, flush the eye immediately, test the pH, check the intraocular pressure and assess the patient at slit lamp to determine extent of damage to the ocular surface. When assessing the damage, the Roper-Hall classification of ocular chemical injuries can be used, which proceeds as follows:[7]

- Grade I—there's damage to the corneal epithelium, no limbal ischemia, and the prognosis is good;
- Grade II—corneal haze is present and iris details are visible; there's less than one-third limbal ischemia and the prognosis remains good;
- Grade III—there's complete loss of the epithelium, stromal haze and the iris details are obscured; there's one-third to one-half limbal ischemia, and the prognosis is guarded;
- Grade IV—the cornea is opaque, and iris and pupil details are obscured; there's greater than one-half limbal

PEDIATRIC OCULAR TRAUMA BY THE NUMBERS

Here's a review of the statistics and common causes of ocular trauma in kids through the years:

Children younger than 4 years of age tend to be most affected by ocular trauma overall. This age group is also more likely to incur injuries with a high risk of vision loss. High-risk injuries in young children are commonly attributed to lapses in caregivers' attention combined with exposure to household cleaners, sharp-edged items around the home or toys with projectile parts.[1] Pediatric eye trauma most commonly occurs in boys at a rate approximately three times higher than in girls.[1,2] Traumatic ocular injuries more frequently occur in children living in large metropolitan regions with populations of over 1 million and in areas with median household incomes falling in the lowest quartile. In addition, most children suffering ocular injuries have public insurance.[1]

In 2000, a study of pediatric eye trauma in the United States found that the majority of injuries occurred as a result of motor vehicle accidents.[3] Over time, the predominant etiology has shifted, as a later study in 2014 determined sports injuries to be the leading cause of eye trauma in children.[1] The change is largely attributed to a decrease in vehicle-related injuries due to legislation passed beginning in 1993 that increased automotive safety by mandating upgrades in head protection, airbags and appropriate restraints for children under 8 years of age.[1] Additionally, there was a 26.1-percent decrease in the overall number of ED visits for pediatric eye injuries from 2006 to 2014, suggesting that such mandates were instrumental in decreasing the incidence of pediatric ocular trauma.[1] This large decrease may also be partly explained by a decrease in pediatric gun-related eye injuries. An earlier study conducted from 1990 to 2012 showed injuries due to non-powder guns had increased by 168.8 percent and accounted for almost half of all pediatric ocular trauma hospitalizations.[2] However, more recent data suggests this trend is changing as a 68.5-percent decline in such injuries was seen from 2006 to 2014.[1]

While overall numbers of ocular trauma injuries in the pediatric population may be decreasing, several types of ocular injury are on the rise. In particular, sports-related injuries have been found to be increasing in prevalence, with basketball, football, baseball and softball as the most common causes.[1,2] Participation in sports and recreational activities is immensely beneficial to children physically, socially and psychologically but puts them at risk of injury. With the use of appropriate eyewear and protection, however, it's estimated that around 90 percent of sports-related eye trauma in children is preventable.[2]

Eye injuries from household/domestic activities and pet-related injuries are also on the rise. From 2006 to 2014, injuries resulting from pet-related incidents increased by 16.9 percent, while other home-related causes of eye injury increased by 29.6 percent. Other sources of injury in the home include common household items such as cleaning fluids and automotive chemicals. Substances with colorful packaging are especially enticing to children, and while child-resistant mechanisms, printed warnings and age recommendations are proven prevention strategies, parents must still take care to safely store such items in a way that reduces accessibility, and properly dispose of harmful items.[1] This is particularly relevant with the onset of the COVID-19 pandemic, as children are spending significantly more time at home, which increases the chance of exposure to such substances.

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ischemia and the prognosis is poor.

Once you've classified the injury, you—or in severe cases, a corneal specialist—can begin treatment based on the severity. Based on recommendations from the American Academy of Ophthalmology,[8] treatment consists of the following:

For grade I injuries:

- topical antibiotic ointment (erythromycin ointment or similar) four times a day;
- prednisolone acetate 1% four times a day;
- preservative-free artificial tears as needed; and
- for pain, consider a short-acting cycloplegic like cyclopentolate three times a day.

For grade II injuries:

- topical antibiotic drop four times daily;
- prednisolone acetate 1% hourly while awake for the first seven to 10 days. Consider tapering the steroid if the epithelium has not healed by around day 10 to 14. If an epithelial defect persists after day 10, consider progestational steroids (1% medroxyprogesterone four times daily);
- long-acting cycloplegic like atropine;
- oral Vitamin C, 2 g four times a day;
- doxycycline, 100 mg twice a day (avoid in children, however);
- sodium ascorbate drops (10%) hourly while awake;
- preservative-free artificial tears as needed; and
- debridement of necrotic epithelium and application of tissue adhesive as needed.

If a patient has a grade III injury:

- all the treatments done for Grade II; and
- possible amniotic membrane transplant, best performed in the first week after injury. Recommendations are to place the amniotic membrane so that it covers the palpebral conjunctiva by suturing it to the lids in the operating room, not just covering the cornea and bulbar conjunctiva with it.

For grade IV:

- The same approaches as for grade II/III; and
- early surgery is usually necessary.

If there's significant necrosis, a tenonplasty can help reestablish the limbal vessels. An amniotic membrane transplant is often necessary due to the severity of the damage.

Physical Abuse and Neglect

Other potential sources of pediatric ocular trauma during the pandemic may arise due to the added stresses on caregivers. Due to people losing their sources of income, social isolation and school closures, many families are facing dramatically heightened levels of stress. Physicians and families must be cognizant of the fact that with added stress comes increased risk of child abuse and neglect.

A study conducted from January 2019 to September 2020 found the percentage of ED visits related to child abuse and neglect ending in hospitalization has increased significantly among children and adolescents under 18.[9]

If a child presents with trauma to the ocular region, be aware of the following key signs that could possibly indicate abuse:

- retinal hemorrhages, which are seen in approximately 75 percent of abuse cases involving head trauma (indirect ophthalmoscopy, ideally with dilation, will help identify these);
- acquired strabismus from increased intracranial pressure from injury;
- traumatic hyphema;
- Marcus Gunn pupil;
- periorbital ecchymosis;
- subconjunctival hemorrhages; and/or
- changes in mental status with no obvious cause.[10]

With the above signs in mind, medical personnel must maintain suspicion for possible child abuse and appropriately report abuse to the authorities when identified.

In conclusion, the COVID-19 pandemic has brought unprecedented changes to health care. While prepandemic data suggests the incidence of pediatric ocular trauma appears to be decreasing overall, COVID-19 has dramatically changed the way we live and therefore the risks we face each day that may impact our health. As ocular trauma is a leading cause of visual loss in the pediatric population, it's imperative for physicians and parents to remain vigilant, particularly during the pandemic, as conditions continue to change with the introduction of vaccines and attempts to return to a new state of normalcy. ◀

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ABOUT THE AUTHORS

Ms. Casella is a pursuing a medical degree at the Miller School of Medicine. **Dr. Cavuoto** practices at the University of Miami's Bascom Palmer Eye Institute, and is an associate professor of clinical ophthalmology at the University of Miami Miller School of Medicine. They report no relationships with companies that make products mentioned in this article.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA® (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

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 latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA 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 VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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*Pivotal study designs: Two Phase 3, randomized, multicenter, parallel-group studies, APOLLO and LUNAR, evaluating noninferiority of once-daily VYZULTA vs twice-daily timolol maleate 0.5% in patients with open-angle glaucoma or ocular hypertension. Primary endpoint was IOP measured at 9 assessment time points in study eye. APOLLO (VYZULTA, n=284; timolol, n=133) and LUNAR (VYZULTA, n=278; timolol, n=136).[2,3]

INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. **2.** Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology.* 2016;123(5):965-973. **3.** Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol.* 2016;168:250-259.

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